CORN REFINERS
ASSOCIATION

October 24, 2008

Ms. Carole Davis
Co-Executive Secretary of the Dietary Guidelines Advisory Committee
Center for Nutrition Policy and Promotion
U.S. Department of Agriculture
3101 Park Center Drive, Room 1034
Alexandria, VA 22302

Dear Ms. Davis:

The Corn Refiners Association, on behalf of its members, is pleased to submit the following peer-reviewed research on high fructose corn syrup in response to the Dietary Guidelines Advisory Committee's Solicitation of Written Comments as published in the October 14, 2008, *Federal Register* (vol. 73, no. 199, pp. 60672-60673).

<u>General Information Regarding High Fructose Corn Syrup</u>

61 *Federal Register* 43447 (August 23, 1996), 21 C.F.R. 184.1866. Direct Food Substances Affirmed as Generally Recognized as Safe; High Fructose Corn Syrup – Final Rule.

53 *Federal Register* 44904 (November 7, 1988), 21 C.F.R. 182.1866. Proposed Affirmation of GRAS Status of High Fructose Corn Syrup – Proposed Rule.

48 *Federal Register* 5716 (Feb 8, 1983), 21 C.F.R. 182.1866. Substances Generally Recognized as Safe; High Fructose Corn Syrup and Insoluble Glucose Isomerase Enzyme Preparations-Final Rule.

Coulston, A.M. and Johnson, R.K. 2002. Sugar and Sugars: Myths and realties. *Journal of the American Dietetic Association.* 102(3):351-353.

Hanover, L.M. and White, J.S. 1993 Manufacturing, composition, and applications of fructose. *American Journal of Clinical Nutrition* 58(suppl 5):724S-732S.

Hein, G.L., Storey M.L., White, J.S., and Lineback, D.R. 2005. Highs and Lows of High Fructose Corn Syrup: A Report From the Center for Food and Nutrition Policy and Its Ceres® Workshop. *Nutrition Today* 40(6):253-256, November/December 2005.

Schorin, M.D. 2005. High Fructose Corn Syrups, Part 1: Composition, Consumption, and Metabolism. *Nutrition Today* 40(6): 248-252, November/December 2005.

Schorin, M.D. 2005. High Fructose Corn Syrups, Part 2: Health Effects. *Nutrition Today* 41(2):70-77, March/April 2006.

White, J.S. 2008. Straight talk about high-fructose corn syrup: what it is and what it ain't. *American Journal of Clinical Nutrition* 88(suppl): in press.

High Fructose Corn Syrup and Metabolism

Lowndes, J., Zuckley, L.M., Nguyen, V., Angelopoulos, T.J., and Rippe, J.M. June 2007. The Effect of High-Fructose Corn Syrup on Uric Acid Levels in Normal Weight Women. Presented at the annual meeting of the Endocrine Society June 2-5, 2007. Program Abstract #P2-45.

Melanson, K.J., Zuckley, L., Lowndes J., Nguyen, V., Angelopoulos, T.J., and Rippe, J.M. 2007. Effects of high-fructose corn syrup and sucrose consumption on circulating glucose, insulin, leptin, and ghrelin and on appetite in normal-weight women. *Nutrition* 23:103-112.

Zuckley, L.M., Lowndes, J., Melanson, K.J., Nguyen, V., Angelopoulos, T.J., and Rippe, J.M. June 2007. The Effect of High Fructose Corn Syrup on Post-Prandial Lipemia in Normal Weight Females. Presented at the June 2007 Meeting of The Endocrine Society. Program Abstract #P2-46.

High Fructose Corn Syrup and Satiety

Akhavan, T. and Anderson, G.H. 2007. Effects of glucose-to-fructose ratios in solutions on subjective satiety, food intake, and satiety hormones in young men. *American Journal of Clinical Nutrition* 86:1354-1363.

Almiron-Roig, E. and Drewnowski, A. September 2003. Hunger, thirst, and energy intakes following consumption of caloric beverages. *Physiology & Behavior* 79 (4-5):767-773.

Melanson, K.J., Angelopoulos, T.J., Nguyen, V., Zukley L., Lowndes J., and Rippe, J.M. 2008. High-fructose corn syrup, energy intake, and appetite regulation. *American Journal of Clinical Nutrition* 12(suppl): in press.

Soenen, S. and Westerterp-Plantenga, M.S. 2007. No differences in satiety of energy intake after high-fructose corn syrup, sucrose, or milk preloads. *American Journal of Clinical Nutrition* 86(1):1586-1594.

High Fructose Corn Syrup and Sugar

Monsivais P., Perrigue, M.M., and Drewnowski, A. 2007. Sugars and satiety: does the type of sweetener make a difference? *American Journal of Clinical Nutrition* 86:116-123.

High Fructose Corn Syrup and Weight Gain

Forshee, R.A., Storey, M.L., Allison, D.B., Glinsmann, W.H., Hein, G.L., Lineback, D.R., Miller, S.A., Nicklas, T.A., Weaver, G.A., and White, J.S. 2007. A Critical Examination of the Evidence Relating High Fructose Corn Syrup and Weight Gain. *Critical Reviews in Food Science and Nutrition* 47(6):561-582.

Sun, S.Z. and Empie, M.W. 2007. Lack of findings for the association between obesity risk and usual sugar-sweetened beverage consumption in adults – A primary analysis of databases of CSFII-1989-1991, CSFII-1994-1998, NHANES III, and combined NHANES 1999-2002. *Food Chemical Toxicology* 45(8):1523-1536.

Miscellaneous High Fructose Corn Syrup Research

Skoog, S.M., Bharucha, A.E., and Zinsmeister, A.R. May 2008. Comparison of breath testing with fructose and high fructose corn syrups in health and IBS. *Neurogastroenterology & Motility* 20(5) 505-511.

Wheeler, M.L. and Pi-Sunyer, F. Xavier. April 2008. Carbohydrate Issues: Type and Amount. *Journal of the American Dietetic Association*108 (4)(suppl): S34-S39.

We hope this research will be helpful as you consider the 2010 Dietary Guidelines.

We also wish to draw your attention to two important determinations made about high fructose corn syrup in 2008:

- In June, the American Medical Association concluded after a year-long study, "high fructose syrup does not appear to contribute to obesity more than other caloric sweeteners." American Medical Association press release, June 17, 2008.

- In July, the U.S. Food and Drug Administration clarified its position regarding use of the term 'natural' for products sweetened with high fructose corn syrup. The Food and Drug Administration stated, referring to a process commonly used by the corn refining industry, that it "would not object to the use of the term 'natural' in a product containing HFCS produced by [that] manufacturing process." Geraldine A. June, Supervisor, Product Evaluation and Labeling Team, Center for Food Safety and Applied Nutrition (Letter to Corn Refiners Association, July 3, 2008).

Please do not hesitate to contact me at (202) 331-1634 or at aerickson@corn.org should you have any questions concerning the enclosed research.

Sincerely,

AErickson

Audrae Erickson
President

Enclosures

General Information Regarding High Fructose Corn Syrup

61 *Federal Register* 43447 (August 23, 1996), 21 C.F.R. 184.1866. Direct Food Substances Affirmed as Generally Recognized as Safe; High Fructose Corn Syrup – Final Rule.

53 *Federal Register* 44904 (November 7, 1988), 21 C.F.R. 182.1866. Proposed Affirmation of GRAS Status of High Fructose Corn Syrup – Proposed Rule.

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Schorin, M.D. 2005. High Fructose Corn Syrups, Part 1: Composition, Consumption, and Metabolism. *Nutrition Today* 40(6): 248-252, November/December 2005.

Schorin, M.D. 2005. High Fructose Corn Syrups, Part 2: Health Effects. *Nutrition Today* 41(2):70-77, March/April 2006.

White, J.S. 2008. Straight talk about high-fructose corn syrup: what it is and what it ain't. *American Journal of Clinical Nutrition* 88(suppl): in press.

61 *Federal Register* 43447 (August 23, 1996), 21 C.F.R. 184.1866. Direct Food Substances Affirmed as Generally Recognized as Safe; High Fructose Corn Syrup – Final Rule.

(3) The claim may indicate that oral hygiene and proper dental care may help to reduce the risk of dental disease.

(4) The claim may indicate that the sugar alcohol serves as a sweetener.

(e) *Model health claim*. The following model health claims may be used in food labeling to describe the relationship between sugar alcohol-containing foods and dental caries.

(1) Example of the full claim:

(i) Frequent eating of foods high in sugars and starches as between-meal snacks can promote tooth decay. The sugar alcohol [name, optional] used to sweeten this food may reduce the risk of dental caries.

(ii) Frequent between-meal consumption of foods high in sugars and starches promotes tooth decay. The sugar alcohols in [name of food] do not promote tooth decay.

(2) Example of the shortened claim for small packages:

(i) Does not promote tooth decay.

(ii) May reduce the risk of tooth decay.

Dated: August 16, 1996.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 96-21481 Filed 8-20-96; 8:53 am]

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21 CFR Parts 182 and 184

[Docket No. 85N-0548]

Direct Food Substances Affirmed as Generally Recognized as Safe; High Fructose Corn Syrup

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations for substances that are generally recognized as safe (GRAS) to affirm that high fructose corn syrup (HFCS), prepared from high dextrose equivalent corn starch hydrolysate by partial enzymatic conversion of glucose (dextrose) to fructose utilizing one of several glucose isomerase enzyme preparations, is GRAS as a direct human food ingredient. This action is in response to six petitions filed by members of the food industry.

DATES: Effective August 23, 1996. The Director of the Office of the Federal Register approves the incorporation by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51 of a certain publication in 21 CFR 184.1866, effective August 23, 1996.

FOR FURTHER INFORMATION CONTACT: James C. Wallwork, Center for Food Safety and Applied Nutrition (HFS-217), Food and Drug Administration, 200 C St. SW., Washington, DC 20204-0001, 202-418-3078.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of February 8, 1983 (48 FR 5716), FDA published a document that listed HFCS as GRAS for use in food (§ 182.1866 (21 CFR 182.1866)) and also affirmed that certain insoluble glucose isomerase enzyme preparations are GRAS for use in the manufacture of HFCS (§ 184.1372 (21 CFR 184.1372)) (hereinafter referred to as the 1983 final rule). The agency published this final rule in response to six industry petitions that requested GRAS affirmation for certain insoluble glucose isomerase enzyme preparations used to make HFCS and for the manufactured product itself.

The basis for listing HFCS in 21 CFR part 182 was that HFCS is made with enzyme preparations that FDA has affirmed as GRAS; the saccharide composition (glucose to fructose ratio) of HFCS is approximately the same as that of honey, invert sugar, and the disaccharide sucrose; and the minor components (primarily higher saccharides of glucose) of HFCS are also found at similar levels in corn syrup and corn sugar which are already on the GRAS list. Therefore, FDA concluded that it was appropriate to list HFCS as GRAS for use in food while the agency fully evaluated it during the comprehensive safety review of corn sugar, corn syrup, invert sugar, and sucrose.

In the 1983 final rule, the agency gave notice to all interested parties that when the agency completed its comprehensive safety review of corn sugar (dextrose), corn syrup, invert sugar, and sucrose, it would examine the data on these substances to determine whether those data provide an adequate basis to affirm that HFCS is GRAS. In the Federal Register of November 7, 1988 (53 FR 44862), the agency published a final rule affirming that the use of corn sugar, corn syrup, invert sugar, and sucrose in food is GRAS.

II. The Safety Review of High Fructose Corn Syrup

In the Federal Register of November 7, 1988 (53 FR 44904), FDA proposed to affirm that the use of HFCS in food is GRAS (hereinafter referred to as the 1988 HFCS proposal). Included in the 1988 HFCS proposal was the agency's: (1) Evaluation of the data contained in the petitions and of their relationship to the safety of HFCS; (2) discussion of the relevancy of reports by the Select Committee on GRAS Substances of the Federation of American Societies for Experimental Biology entitled "Evaluation of the Health Aspects of Corn Sugar (Dextrose), Corn Syrup, and Invert Sugar as Food Ingredients" (Ref. 1) and "Evaluation of the Health Aspects of Sucrose as a Food Ingredient" (Ref. 2) to the safety assessment of HFCS; and (3) discussion of the relevancy of FDA's Sugars Task Force Report "Evaluation of the Health Aspects of Sugars Contained in Carbohydrate Sweeteners" (Ref. 3) to the safety evaluation of HFCS.

The agency made it clear during its safety evaluation of corn sugar, corn syrup, invert sugar, and sucrose that its exposure estimate for HFCS included exposure to HFCS containing 55 percent fructose (HFCS-55) (Ref. 3). Furthermore, FDA noted that most of the components found in HFCS than 95.0 percent total saccharides (dry weight), of which not less than 55.0 percent onsists of fructose (dry weight), not less than 95.0 percent consists of monosaccharides, and not more than 5.0 percent (dry weight) of other saccharides. Arsenic (as As), not more than 1 milligram per kilogram. Color, within the range specified by the vendor. Heavy metals (as Pb), not more than 5 milligrams per kilogram. Lead, not more than 0.1 milligram per kilogram. Sulfur dioxide, not more than 0.003 percent. Total solids, 42 percent high fructose corn syrup: not less than 70.5 percent. 55 Percent high fructose corn syrup: not less than 76.5 percent."

This information is similar to that published in Food Chemicals Codex, 4th ed., p. 191 (1996), in the monograph entitled "High-Fructose Corn Syrup."

FDA has reviewed the comments and acknowledges that the item of commerce is HFCS-42. The agency agrees with the identity and specifications recommended by the latter comment for HFCS (HFCS-42 or HFCS-43). FDA concludes that the identity and specifications that it is adopting are adequate to ensure that the public health is protected.

The agency also has reviewed the comments from the three trade associations requesting the inclusion of HFCS-55 in the final rule. FDA notes that the comments provided detailed information on the manufacture of HFCS-55, including information on processing aids and residues of these materials in the final product. In addition, the comments provided information on the identity of, and specifications for, the HFCS-55 product.

FDA concludes that the manufacturing process for HFCS-55 does not raise any safety concerns, and that the residues of the processing materials in this product are safe, because HFCS-55 is prepared from HFCS-42 using standard techniques. In addition, as noted earlier in this final rule, the agency has determined that the safety evaluation of the major components in HFCS-42 is also applicable to HFCS-55. Thus, FDA finds that information provided by the comments is sufficient for the agency to include HFCS-55 in the final rule. Accordingly FDA has modified the final rule to include HFCS-55.

The agency has also reviewed the identity and specifications suggested for HFCS-55 in the comments. FDA concludes that the suggested identity and specifications are adequate to ensure that the public health will be protected.

In addition, the agency has determined that because the components of HFCS-55 are similar to HFCS-42, and there are no safety concerns with these components, there is no need to differentiate between these two HFCS's on product labels for consumers.

3. A comment from a trade association included a recommendation for FDA to adopt the Food Chemicals Codex (3d ed., 2d supplement) assay requirements for HFCS. The association also pointed out that the Food Chemicals Codex has published food grade specifications for HFCS.

In the 1988 HFCS proposal, the agency stated that it would cooperate with the National Academy of Sciences to establish specifications for HFCS. The 1988 HFCS proposal also stated that when acceptable specifications are developed, the agency will incorporate them into the regulation. Recently, however, as stated above, industry submitted a comment suggesting new identities and specifications for HFCS-42 and HFCS-55 that are similar to those published in the Food Chemicals Codex, 4th ed., p. 191 (1996), in the monograph entitled "High-Fructose Corn Syrup." These identities and specifications, as discussed in response to comment 2 of this document, are acceptable to the agency and are therefore incorporated by reference.

IV. Conclusion

Based on the conclusions of the Federation of American Societies for Experimental Biology on the safety evaluations of corn sugar, corn syrup, invert sugar, and sucrose (Refs. 1 and 2) and of FDA's Task Force Report on the health aspects of sugars contained in carbohydrate sweeteners (Ref. 3), in the 1988 HFCS proposal, the agency proposed to affirm that the use of HFCS in food is GRAS. FDA has considered all the comments received on the 1988 HFCS proposal and has found that no information has been submitted in response to the proposal that warrants a change in FDA's tentative conclusion about the safety of HFCS or about whether it is GRAS.

The agency agrees with comments to the 1988 HFCS proposal that the item of commerce is HFCS containing not less than 42 percent fructose. Thus, FDA has included HFCS containing not less than 42 percent fructose dry weight in the description of the identity of HFCS in the final rule. In addition, FDA has incorporated by reference the other aspects of the identity and specifications for HFCS-42 that were published in the Food Chemicals Codex, 4th ed., p. 191 (1996), in the monograph entitled "High-Fructose Corn Syrup" and that are similar to industry comments to the 1988 HFCS proposal.

Also, sufficient information was submitted in the comments to justify affirming HFCS-55 as GRAS and to provide specifications for this substance. Therefore, the agency has included HFCS containing not less than 55 percent fructose dry weight in the description of the identity of HFCS in the final rule. In addition, FDA has incorporated by reference the other aspects of the identity and specifications for HFCS-55 that were published in the Food Chemicals Codex, 4th ed., p. 191 (1996), in the monograph entitled "High-Fructose Corn Syrup," and that are similar to industry comments to the 1988 HFCS proposal. Furthermore, the agency is including a sentence in the regulation to characterize the manufacturing process that converts HFCS-42 to HFCS-55, i.e., "The product containing more than 50 percent (dry weight) fructose may be prepared through concentration of the fructose portion of the mixture containing less than 50 percent fructose."

Thus, FDA is including two types of HFCS in this final rule. HFCS-42 contains at least 42 percent fructose, approximately 50 percent glucose, and not more than 8 percent other saccharides. HFCS-55 contains at least 55 percent fructose, approximately 40 percent glucose, and not more than 5 percent other saccharides. HFCS-42 and HFCS-55 both contain similar saccharide compositions (glucose to fructose ratio) as honey, invert sugar, and the disaccharide sucrose, and the minor components (primarily higher saccharides of glucose) of HFCS-42 and HFCS-55 are also present at similar levels in corn syrup and corn sugar, which FDA has already found to be GRAS.

FDA has previously considered the environmental effects of this rule as announced in the 1988 HFCS proposal. FDA did not receive any information or comments that would affect the agency's determination that there is no significant impact on the human environment and that an environmental impact statement is not required.

V. Analysis of Impacts

FDA has examined the economic implications of the final rule affirming the GRAS status of HFCS, prepared from high dextrose-equivalent corn starch hydrolysate by partial enzymatic conversion of glucose (dextrose) to fructose utilizing one of several glucose isomerase enzyme preparations, for use as a direct human food ingredient, under Executive Order 12866 and the Regulatory Flexibility Act. Executive Order 12866 directs agencies to assess

53 *Federal Register* 44904 (November 7, 1988), 21 C.F.R. 182.1866. Proposed Affirmation of GRAS Status of High Fructose Corn Syrup – Proposed Rule.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 182 and 184

[Docket No. 85N-0548]

Proposed Affirmation of GRAS Status of High Fructose Corn Syrup

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to affirm that high fructose corn syrup is generally recognized as safe (GRAS) as a direct human food ingredient. The safety of this ingredient has been evaluated on the basis of the agency's evaluation of six industry petitioners and of the agency's comprehensive safety review of corn sugar, corn syrup, invert sugar, and sucrose. Published elsewhere in this issue of the Federal Register is a final rule affirming the GRAS status of corn sugar, corn syrup, invert sugar, and sucrose.

DATE: Written comments by January 6, 1989.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 230857.

FOR FURTHER INFORMATION CONTACT: John W. Gordon, Center for Food Safety and Applied Nutrition (HFF-334), Food and Drug Administration, 200 C Street SW., Washington, DC 20204, 202-426-5487.

SUPPLEMENTARY INFORMATION:

I. Introduction

A. Listing of High Fructose Corn Syrup as GRAS in Part 182

In the Federal Register of February 8, 1983 (48 FR 5716, FDA published a regulation in 21 CFR Part 182 that listed high fructose corn syrup as GRAS for use in food. FDA published this regulation in response to six industry petitions that requested GRAS status for certain insoluble glucose isomerase enzyme preparations used to make high fructose corn syrup and for the manufactured product itself.

The basis for listing high fructose corn syrup in Part 182 was that (1) this substance is made with enzyme preparations that the agency had affirmed as GRAS, and (2) the saccharide composition (glucose to fructose ratio) of high fructose corn syrup is approximately the same as that of honey, invert sugar, and the disaccharide sucrose. In addition, the minor components (primarily higher saccharides of glucose) of high fructose corn syrup are also found at similar levels in corn syrup and corn sugar which are already on the GRAS list. Therefore, FDA concluded that high fructose corn syrup is as safe for use in food as sucrose, corn sugar, corn syrup, and invert sugar. However,, because the agency had not made a decision on whether it would affirm the latter ingredients as GRAS, it could not make this decision for high fructose corn syrup at that time.

The agency stated that when it completed its comprehensive safety review of corn sugar (dextrose), corn syrup, invert sugar, and sucrose, it would determine whether the data on these substances provided an adequate basis to affirm the GRAS status of high fructose corn syrup.

B. Identity of High Fructose Corn Syrup

Paragraph (a) of 21 CFR 182.1866 describes high fructose corn syrup as "a sweet, nutritive saccharide mixture containing approximately 52 percent (dry weight) glucose, 43 percent (dry weight) fructose, and 5 percent (dry weight) other saccharides. It is prepared as a clear aqueous solution from high dextrose equivalent corn syrup hydrolystate by partial enzymatic conversion of glucose (dextrose) to fructose using an insoluble glucose isomerase enzyme preparation described in § 184.1374 of this chapter."

The proposed regulation applies only to the high fructose corn syrup that meets the description as specified in 21 CFR 182.1866(a). The agency is aware that there are other products on the market that are also called "high fructose corn syrup" but that have fructose contents of greater than 43 percent (dry weight). These products generally contain either 55 percent fructose (HFCS-55) or 90 percent fructose (HFCS-90) on a dry weight basis. FDA is not proposing to affirm, these products as GRAS because, as discussed later in this document, their manufacture involves the use of processing materials that are not used in making the 43 percent fructose product, and the agency does not have adequate information on these materials to assess the safety of their residual levels in these products.

C. Definitions

To clarify its discussion of the proposed GRAS affirmation of high fructose corn syrup, the agency is defining and explaining important terms used in this document.

The term "sugar" is used to refer to any of the mono- and disaccharides glucose, fructose, sucrose, and maltose, which are found in sucrose, corn sugar, corn syrup, invert sugar, and high fructose corn syrup. The term "sugar" has traditionally been used by consumers and by the agency (see 21 CFR 145.3(f), 146.3(f), and 170.3(n)(41)) as a synonym for the sweetener sucrose. In this document, however the sweetener sucrose is identified as "sucrose." The agency will use the term "sugars" to describe mixtures of mono- and disaccharides and collectively all forms of sugar present in a food.

FDA will use the term "sweetener" to refer to any one or more of the carbohydrate food ingredients sucrose, corn sugar, corn syrup and solids, invert sugar, high fructose corn syrup, honey, and other edible syrups. The term "sweetener", as used in this document, is not intended to include any other nutritive or nonnutritive sweeteners that are added to food.

High fructose corn syrup, as described earlier, is composed primarily of approximately equimolar amounts of the monosaccharides glucose and fructose with some higher molecular weight saccharides. Sucrose is the disaccharide of glucose and fructose. Invert sugar is composed of glucose, fructose, and sucrose. Corn sugar, commonly referred to as dextrose, is crystalline α-D-glucose. Corn syrup contains glucose and maltose (a disaccharide of glucose), as well as higher molecular weight saccharides. These five ingredients may also contain water and residues from the carbohydrate source material and from processing.

II. The Safety Review of High Fructose Corn Syrup

A. Sources of Information for the Safety Evaluation of High Fructose Corn Syrup

In evaluating the safety of high fructose corn syrup as a GRAS ingredient, the agency used the following sources of information:

1. GRAS Affirmation Petitions on High Fructose Corn Syrup (4G0042, 6G0060, 7G0080, 7G0084, 7G0086, and 1G0271)

These petitions describe high fructose corn syrup as a mixture of sugars, including approximately 52 percent glucose (dextrose), 43 percent fructose, and 5 percent maltose, isomaltose, and other sugars that are natural components of corn syrup. The petitions stated that high fructose corn syrup is made by the action of a glucose isomerase enzyme preparation on high dextrose equivalent corn syrup.

Each of the five petitions requested GRAS affirmation for a specific glucose isomerase preparation derived from one of five microbial species. The identity of the enzyme preparation was based on the identity of the microbial source and the identity of the materials used to produce and immobilize the enzyme preparation.

The petitions provided precise taxonomic classification of each microbial source. The petitions contained information that described the method and materials used to produce and to immobilize the enzyme-containing cellular materials.

The petitions contained general manufacturing information for high fructose corn syrup that provides a basis upon which to determine the residual levels of enzyme preparation that would occur in high fructose corn syrup. This information demonstrated that, under the current methods, only very small amount of enzyme preparation would enter the product. The enzyme preparation is extensively washed to remove processing materials before it is used. In addition, only relatively small amounts of the washed enzyme preparation are used to catalyze the conversion of large quantities of glucose syrup.

The petitions also contained published data on the microbial sources of the enzyme preparation as well as unpublished animal feeding studies that established safe levels of the enzyme preparation in the product. A more detailed discussion of the identity of high fructose corn syrup, of its method of manufacture, and of the rationale for the agency's safety determination for the enzyme preparations used in the manufacture of high fructose corn syrup is found in the final rule published in the Federal Register of February 8, 1983 (48 FR 5716).

2. The Select Committee Report: "Evaluation of the Health Aspects of Corn Sugar (Dextrose), Corn Syrup, and Invert Sugar as Food Ingredients" (SCOGS-50) (Ref. 1)

This report is relevant to the safety of high fructose corn syrup because any adverse health effects associated with the consumption of corn sugar, corn syrup, and invert sugar are likely also to be associated with high fructose corn syrup. High fructose corn syrup, corn sugar, and corn syrup all contain glucose, maltose, and higher saccharides, as well as residues from the processing aids and from the corn used to manufacture these sweeteners. Both high fructose corn syrup and invert sugar contain glucose and fructose. Therefore, any adverse health effect of consumption of corn sugar, corn syrup, or invert sugar may also occur from consumption of high fructose corn syrup.

The report of the Select Committee also contains a limited opinion and conclusion regarding the safety of high fructose corn syrup. The report states that the consumption of dextrose and corn syrup has increased markedly in recent years and a major part of the increase resulted from the introduction of high fructose corn syrup. The Select Committee cited predictions that high fructose corn syrup would replace 30 percent of the applications for sucrose and invert sugar. In the opinion of the Select Committee there is no evidence such replacement would have an adverse effect on public health. A more detailed description of the findings and the conclusions of the Select Committee on the safety of corn sugar, corn syrup, and invert sugar was published in the agency's proposal to affirm the GRAS status of these food ingredients (47 FR 53917; November 30, 1982).

3. The Select Committee Report: "Evaluation of the Health Aspects of Sucrose as a Food Ingredient" (SCOGS-69) (Ref. 2)

Sucrose is a disaccharide that is hydrolyzed in the intestine and is absorbed as its component monosaccharides, glucose and fructose. High fructose corn syrup also is essentially a mixture of glucose and fructose in approximately equal proportions. Because of the similarity in sugars composition between these two sweeteners at the time of absorption, any reported adverse health effects of sucrose consumption are likely to occur also from consumption of high fructose corn syrup. Thus, the Select Committee's report on sucrose is relevant to the safety evaluation of high fructose corn syrup. A description of the findings and the conclusions of the Select Committee on the safety of sucrose was published in the agency's proposal to affirm the GRAS status of sucrose as a food ingredient (47 FR 53923; November 30, 1982).

4. The Task Force Report: "Evaluation of Health Aspects of Sugars Contained in Carbohydrate Sweeteners" (Ref. 3)

In November 1983, the agency established the Sugars Task Force composed of scientists from FDA's Center for Food Safety and Applied Nutrition to update the Select Committee's safety reviews of corn sugar, corn syrup, and invert sugar and of sucrose.

In its safety evaluations of these substances, the Select Committee found: (1) That the safety of a specific sweetener can be assessed only as part of a safety assessment of total sweetner consumption (see the Select Committee's conclusions for sucrose and for corn sugar, corn syrup, and invert sugar); and (2) that the safety of an individual sweetener is contingent upon the safety of the "simple sugars" that it contains (see especially the Select Committee's conclusion for corn sugar, corn syrup, and invert sugar). Based on these findings, the agency charged the Task Force to conduct a single safety review of all sweeteners.

The Task Force review focused on the sugars contained in the sweeteners rather than on the sweeteners themselves. It used the conclusions it reached on the safety of the sugars to assess the safety of the sweeteners that contain these sugars.

The Task Force has completed its safety review. FDA has placed a copy of the Task Force's report on file in the Dockets Management Branch (address above) in Docket No. 76N-0141. This report contains safety data on fructose, glucose, maltose, and sucrose that are relevant to a safety assessment of high fructose corn syrup. It also contains an assessment of various sugars intakes and sweetener availability and thereby provides a basis for estimating current consumption of high fructose corn syrup.

A more complete description of the Task Force's safety review and of the conclusions of the Task Force regarding the safety of the dietary sugars (glucose, fructose, sucrose, and maltose) is provided elsewhere in this issue of the Federal Register in the final rule that affirms the GRAS status of corn sugar, corn syrup, invert sugar, and sucrose.

B. Findings of the Safety Review for High Fructose Corn Syrup

1. Consumption of High Fructose Corn Syrup

The Task Force, in its report, estimated that in 1984 the average daily intake of sugars from high fructose corn syrup was 19 grams per person per day, and that for the 90th percentile consumers of total sugars, it was 43 grams per person per day (Ref. 3). Because the sugars in high fructose corn syrup (glucose, fructose, and maltose) represent approximately 98 percent of its dry weight, the agency concludes that these values represent appropriate estimates of the average daily intakes of high fructose corn syrup itself on a dry weight basis.

In its report, the Task Force estimated intakes of the sugars glucose, fructose, sucrose, and maltose by combining food consumption data from the U.S. Department of Agriculture (USDA) Nationwide Food Consumption Survey of 1977-1978 with sugars composition data (Ref. 3). For details of how the Task

Force made its estimate see the final rule, Ref. 2.

It should be noted that the consumer exposure data relating to high fructose corn syrup consumption presented in the Task Force report included current use of HFCS-55. The exposure data, however, did not include HFCS-90 because this product is not currently used in a significant amount, and data required to make intake estimates of this product are not available (Ref. 3).

The Task Force also assessed trends in sweetener availability based on USDA disappearance data. Disappearance data for sweeteners represent estimates of domestic shipments (deliveries) of sweeteners by refiners and importers to primary buyers, such as food industries, trades, wholesalers, and retailers (Ref. 3). The data thus represent approximate estimates of the total amount (dry weight) of sweeteners available for consumptoin by the U.S. population and not the amount of sweeteners actually consumed.

The Task Force's assessment of USDA disappearance data for total sweeteners showed that, since 1970, availability of total sweeteners has been reasonably constant (Ref. 3). The same data show, however, that during this period, there was a significant change in types of sweeteners used. High fructose corn syrup usage increased rapidly, accompanied by a complete decrease in sucrose usage. These data also show that high fructose corn syrup usage has now plateaued, and no further increase is expected in the near future (Ref. 3). Based on this projection, the agency anticipates little future change in exposure to high fructose corn syrup.

2. Safety of High Fructose Corn Syrup

In its reports evaluating the safety of sucrose and the safety of corn sugar, corn syrup, and invert sugar, the Select Committee concluded (Refs. 1 and 2) that sucrose, glucose, and fructose (and therefore corn sugar, corn syrup, high fructose corn syrup, and invert sugar) are cariogenic. However, other than the contribution of dental caries, the Select Committee found no evidence that sucrose, corn sugar, corn syrup, and invert sugar are a hazard to the public when they are used in the manner practiced and at the levels used at the time of the reports. The Select Committee noted, however, that it could not determine whether an increase in total sweetener consumption (the total of sucrose, corn syrup, and invert sugar) would constitute a dietary hazard.

In its report on corn syrup, corn syrup, and invert sugar, the Select Committee also expressed the opinion that (Ref. 1):

> High fructose corn syrups are predicted to increase in production and to replace sucrose and invert sugar in up to 30 percent of their applications by 1980-85, based largely on relative costs. There is no evidence that such replacement, *per se*, would have an adverse effect on public health.

This opinion is based on the assumption that high fructose corn syrups will be formulated in the present manner, i.e., approximately equimolar mixture of glucose and fructose. It does not extend to the use of fructose syrups or other types of high fructose corn syrups that are predominantly fructose, because these syrups may have health effects that differ substantially from the types manufactured currently.

In its report evaluating the safety of sugars (glucose, fructose, sucrose, and maltose), the Task Force concluded that (Ref. 3):

(1) Evidence exists that sugars, as they are consumed in the American diet, contribute to the development of dental caries.

(2) Other than the contribution to dental caries, there is no conclusive evidence in the available information on sugars that demonstrates a hazard to the general public when sugars are consumed at the levels that are now curmet and in the manner now practiced.

The agency evaluated the safety issues related to sweetener consumption raised in the Select Committee's reports on sucrose and on corn sugar, corn syrup, and invert sugar and in the Task Force report. In particular, it considered the issue of the association between consumption of these sweeteners (or sugars) and the incidence of dental caries.

The agency recognized that the Task Force's conclusions regarding dental caries reinforce the Select Committee's conclusions and establish more definitely the association between sugars consumption and dental caries incidence. Yet, the agency decided to affirm the GRAS status of the use of sucrose, corn sugar, corn syrup, and invert sugar, despite their contribution to dental caries formation. The agency concluded that while the Task Force's findings on dental caries supported the Select Committee's findings, the Task Force's findings did not show that the association between sugars consumption and dental caries had become a more significant health problem than it had been in 1976. The Task Force report showed that total exposure to sweeteners had not changed since the Select Committee's report. Moreover, it showed that caries incidence in the United States had declined in the past decade. The data reviewed in the Task Force report suggest that further developments in caries prevention should facilitate this decline in the future.

For these reasons, the agency has concluded that the Task Force's review did not provide any basis for modifying the 1982 proposed GRAS affirmation of corn sugar, corn syrup, invert sugar, and sucrose.

3. Effects of Increased Consumption of Fructose

The major change in sugars consumption that has occurred as a result of the introduction of high fructose corn syrup containing approximately equimolar amounts of glucose and fructose is the increased consumption of glucose and fructose as monosaccharides as opposed to their consumption as the disaccharide sucrose.

The agency has no significant safety concern about the increase in glucose consumption and would be concerned only if this increase was so great as to cause a nutritional imbalance. Glucose is a normal body nutrient and is the main source of energy for living organisms, including humans. Glucose in a polymeric form (starch) is a normal macronutrient in the human diet.

Fructose, however, does not occupy a similar place in the human diet and metabolism. Before the introduction of high fructose corn syrup, the major sources of added dietary fructose were sucrose and honey. Thus, the major question that must be answered in a safety evaluation of high fructose corn syrup is the effect of consumption of high fructose corn syrup on total fructose consumption.

The Task Force considered current levels of fructose intake, the trend in high fructose corn syrup intake, and the health problems that are associated with the current and the anticipated levels of fructose intake.

As part of its safety assessment of fructose, the Task Force estimated the level of consumption of this sugar in 1984 (Ref. 3). It found that the average daily intake of added fructose was 10 grams per day, and that the 90th percentile average daily intake of added fructose was 23 grams per day. The Task Force in its safety evaluation of fructose found that these intake levels are safe (except for contributing to dental caries) based on safety data reviewed for its report (Ref. 3).

The Task Force assessed the changes in availability of fructose added to food. Based on the evaluation of USDA disappearance data, the Task Force found that the availability of high fructose corn syrup increased since

1970. This increase in the high fructose corn syrup usage has resulted in an increase in the availability of fructose added to the food supply. However, the true increase in fructose availability is smaller than that which appears from the increase in the high fructose corn syrup usage because two thirds of the high fructose usage replaced the sucrose usage in soft drinks, and most of the sucrose in soft drinks exists as glucose and fructose (invert sugar), not as sucrose. Thus, part of the increase in fructose availability acutally replaced the fructose that was already existing in the food supply (Ref. 3). Further, the increase in the high fructose corn syrup usage has been accompanied by a comparable decline in the availability of sucrose. Because sucrose splits into glucose and fructose before absorption for use by the body, the total body load of fructose has not changed much due to use of high fructose corn syrup as currently practiced.

C. Conclusions on the GRAS Status of High Fructose Corn Syrup

Based on the findings of the safety reviews of both the Select Committee and the Task Force, the agency finds that evidence exists that high fructose corn syrup, as it is consumed in the average American diet, contributes to the formation of dental caries.

The agency also finds that there is no convincing evidence in the available information on high fructose corn syrup that demonstrates a hazard to the public, other than dental caries, when high fructose corn syrup is consumed at the levels that are now current and in the manner now practiced.

This conclusion is based on the following:

(1) Data in the Task Force report that show that use of high fructose corn syrup has not resulted in an increase in the consumption of total sugars in the United States as a result of the substitution of high fructose corn syrup for other sweeteners, primarily sucrose.

(2) The safety of the monosaccharides (i.e., glucose and fructose) in high fructose corn syrup (containing equimolar amounts of glucose and fructose) is comparable to the safety of sugars in invert sugar. It is also related to the safety of sucrose. Consumption of all three sweeteners results in the absorption and metabolism of glucose and fructose in an approximately equimolar ratio. Thus, consumption of high fructose corn syrup (containing equimolar amounts of glucose and fructose) is not expected to alter the identity, level, or ratio of monosaccharides that are available for absorption and metabolism from the food supply.

(3) Insoluable glucose isomerase enzyme preparations used in the manufacture of high fructose corn syrup arre GRAS (§ 184.1372) (48 FR 5716; February 8, 1983).

(4) The safety of the minor components (e.g., the higher saccharides and other residues from corn and corn processing) of high fractose corn syrup is comparable to the safety of these components in corn sugar and corn syrup (which have been affirmed as GRAS for use in food). These marterials are present in the original corn syrup used to make high fructose corn syrup and their presence and concentration (gram per gram dry weight) are not altered by the high fructose corn syrup manufacturing process.

Based on these findings, the agency tentatively concludes that it can affirm that the high fructose corn syrup described in 21 CFR 182.1866 is generally recognized as safe as a direct human food ingredient.

In reaching this tentative conclusion, the agency notes that its proposed GRAS affirmation of high fructose corn syrup does not cover a major commerical product that is 55 percent (dry weight) fructose, HFCS–55. The petitions on which the GRAS affirmation of high fructose corn syrup is based did not include HFCS–55. However, the agency is aware of the product, and that the manufacture of HFCS–55 includes processing procedures and materials that are not used to prepare the 43 percent fructose HFCS (HFCS–43) that is the subject of this action. The agency has no information on which to assess the identity and possible residue levels of these processing materials in the HFCS–55 final product. Therefore, the agency cannot adequately assess the safety of that product.

The agency's exposure estimate for high fructose corn syrup did, however, include exposure to HFCS–55. Furthermore, the agency concedes that most of the components found in HFCS–43 (approximately equimolar mixtures of glucose and fructose, residues from corn syrup, and residues from the enzyme preparations used to make high fructose corn syrup) are also found in HFCS–55. Therefore, the safety evaluation of the major components in HFCS–43 is also applicable to HFCS–55. Accordingly, the agency would consider including HFCS–55 in its final rule affirming the GRAS status of high fructose corn syrup if it receives, as comments on this proposal, adequate information on how HFCS–55 is manufactured to allow the agency to identify possible residues from processing materials and thereby to ensure that the levels of those residues in the final product are safe.

The proposed GRAS affirmation of high fructose corn syrup also does not include the 90 percent fructose HFCS (HFCS–90), which is also a commercially available product. This product contains a substantially different ratio of glucose to fructose than either HFCS–43 or HFCS–55. HFCS–90 is not included in this rulemaking because the agency does not have adequate information on the processing materials used to make this ingredient to assess the safety of residual levels of the processing materials in the final product. Furthermore, FDA did not inlcude HFCS–90 in the agency's exposure estimate for high fructose corn syrup. The agency is aware of only minor uses of HFCS–90 as an ingredient in low calorie foods. Finally, the agency's safety review of the sugars components of high fructose corn syrup does not cover this product because HFCS–90 does not contain approximately equimolar amounts of glucose and fructose. Thus, additional data on the effects of fructose consumption that is not balanced with glucose consumption would be needed to assure the safety of this product. The agency concludes that appropriate consideration of GRAS status of this product would be through the petition process (21 CFR 170.35).

D. Conditions of GRAS Affirmation

The agency is proposing to affirm the GRAS status of high fructose corn syrup in accordance with 21 CFR 184.1(b)(1). The proposed GRAS affirmation regulation is based on the conclusions of the Select Committee's report and Task Force report on sweeteners.

The agency's conclusion on the use of high fructose corn syrup is based, in large part, on the agency's conclusions on the safety of total sweetener consumption. The agency's conclusion that such consumption is GRAS is predicated on the assumption that the consumption and availability of total sugars will remain at current levels.

Usually when the safety of possible expanded consumption of a substance cannot be ascertained, FDA proposes to establish specific limitations on use of the substance. For corn sugar, corn syrup, invert sugar, and sucrose, however, the agency concluded that limitation on their use would not effectively prevent an increase in total dietary sugars consumption for the following reasons:

(1) The concern of the Select Committee (and of the Task Force) relative to sweetener consumption and

adverse affects was for total sweetener consumption.

(2) The use of these sweeteners is extremely variable within each of the 43 food categories listed in § 170.3(n). Thus, even if the agency were to adopt maximum use levels, it would not prevent manufacturers from increasing the amount of these sweeteners in a particular product in a food category to the level established by the limitation.

(3) Establishment of specific limitations for these sweeteners would not prevent the excessive consumption of these ingredients or other dietary sugars that results from voluntary selection of those foods that have a high sugars content.

For these reasons, the proposed regulations on sucrose, corn sugar, corn syrup, and invert sugar specify that the ingredients are used in food with no limitation other than current good manufacturing practice in accordance with § 184.1(b)(1) (see 47 FR 53917 and 53923; November 30, 1982).

For similar reasons, FDA is proposing to not establish limitations on the use of high fructose corn syrup in food. Given the safety conclusions of both the Select Committee and the Task Force regarding total sweetener consumption, the finding of the Task Force that the level of total sweetener consumption has not changed, and the interchangeability of sweetener use, the agency tentatively concludes that there is no basis for establishing conditions of use for high fructose corn syrup that are different from those established for the other sweeteners. Therefore, the agency is proposing to affirm the GRAS status for the use of high fructose corn syrup in food with no limitation other than current good manufacturing practice. The agency also proposes to amend 21 CFR 184.1372 *Insoluable glucose isomerase enzyme preparations* by removing the Part 182 citation for high fructose corn syrup (21 CFR 182.1866) and replacing this citation with the new Part 184 citation (21 CFR 184.1866).

Food-grade specifications do not exist for high fructose corn syrup at the present time. The agency will work with the Committee on Food Chemicals Codex of the National Academy of Sciences to develop acceptable specifications for this ingredient. When acceptable specifications are developed, the agency will incorporate them into this regulation. Until specifications are developed, FDA has determined that the public health will be adequately protected if commercial high fructose corn syrup complies with the description in the proposed regulation and is of food-grade purity in accordance with 21 CFR 170.30(h)(1) and 182.1(b)(3).

III. Impact Analysis

The agency has determined under 21 CFR 25.24(b)(7) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

FDA, in accordance with the Regulatory Flexibility Act, has considered the effect that this proposal would have on small entities including small businesses and has determined that the effect of this proposal is to maintain current known uses of the substance covered by this proposal by both large and small businesses. Therefore, FDA certifies in accordance with section 605(b) of the Regulatory Flexibility Act that no significant economic impact on a substantial number of small entities will derive from this action.

In accordance with Executive Order 12291, FDA has carefully analyzed the economic effects of this proposal and has determined that the final rule, if promulgated, will not be a major rule as defined by the Order.

The agency's findings of no major economic impact and no significant impact on a substantial number of small entities, and the evidence supporting these findings, are contained in a threshold assessment which may be seen in the Dockets Management Branch.

IV. Comments

Interested persons may, on or before January 6, 1989, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

V. References

The following references have been placed on display in the Dockets Management Branch, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. "Evaluation of the Health Aspects of Corn Sugar (Dextrose), Cron Syrup, and Invert Sugar as Food Ingredients" (SCOGS-50), Select Committee on GRAS Substances, Life Sciences Research Office, Federation of American Societies for Experimental Biology, 1976.

2. "Evaluation of the Health Aspects of Sucrose as a Food Ingredient" (SCOGS-69), Select Committee on GRAS Substances, Life Sciences Research Office, Federation of American Societies for Experimental Biology, 1976.

3. Glinsmann, W. H., Irausquin, H. and Park, Y. K. "Evaluation of Health Aspects of Sugars Contained in Carbohydrate Sweeteners," Report of Sugars Task Force, 1986, *Journal of Nutrition*, 116 (11S):S1–S216, 1986.

4. Kirk-Othmer Encyclopedia of Chemical Technology, 3d Ed., Vol. 22, p. 510.

List of Subjects

21 CFR Part 182

Food ingredients, Food packaging, Spices and flavorings.

21 CFR Part 184

Food ingredients.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that Parts 182 and 184 be amended as follows:

PART 182—SUBSTANCES GENERALLY RECOGNIZED AS SAFE

1. The authority citation for 21 CFR Part 182 continues to read as follows:

Authority: Secs. 201(s), 402, 409, 701, 52 Stat. 1046–1047 as amended, 1055–1056 as amended, 72 Stat. 1784–1788 as amended (21 U.S.C. 321(s), 342, 348, 371); 21 CFR 5.10, 5.61.

§ 182.1866 [Removed]

2. Section 182.1866 *High fructose corn syrup* is removed from Subpart B.

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

3. The authority citation for 21 CFR Part 184 continues to read as follows:

Authority: Secs. 201(s), 402, 409, 701, 52 Stat. 1046–1047 as amended, 1055–1056 as amended, 72 Stat. 1784–1788 as amended (21 U.S.C. 321(s), 342, 348, 371); 21 CFR 5.10, 5.61.

4. Section 184.1372 is amended by revising the first sentence in paragraph (a) to read as follows:

§ 184.1372 Insoluable glucose isomerase enzyme preparations.

(a) Insoluable glucose isomerase enzyme preparations are used in the production of high fructose corn syrup as described in § 184.1866 of this chapter. * * *

* * * * *

5. Section 184.1866 is added to Subpart B to read as follows:

§ 184.1866 High fructose corn syrup.

(a) High fructose corn syrup is a sweet, nutritive saccharide mixture containing approximately 52 percent (dry weight) glucose, 43 percent (dry weight) fructose, and 5 percent (dry weight) other saccharides. It is prepared as a clear aqueous solution from high dextrose equivalent corn starch hydrolysate by partial enzymatic conversion of glucose (dextrose) to fructose utilizing an insoluble glucose isomerase enzyme preparation described in § 184.1372.

(b) FDA is developing food-grade specifications for high fructose corn syrup in cooperation with the National Academy of Sciences. In the interim, this ingredient must be of purity suitable for its intended use.

(c) In accordance with § 184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice.

Dated: October 31, 1988.

John M. Taylor,

Associate Commissioner for Regulatory Affairs.

[FR Doc. 88-25584 Filed 11-4-88; 8:45 am]

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DEPARTMENT OF DEFENSE

Office of the Secretary

32 CFR Part 199

[DoD 6010.8-R]

Civilian Health and Medical Program of the Uniformed Services (CHAMPUS); Application of the Medicare Economic Index

AGENCY: Office of the Secretary, DoD.

ACTION: Proposed rule.

SUMMARY: This proposed rule will amend Part 199 of Title 32, the regulation which governs CHAMPUS, by implementing Section 8019 of the Department of Defense Appropriation Act for 1989, Pub. L. 100-463. This section limits increases in the CHAMPUS prevailing charges for physician and other authorized individual providers of medical care to the extent justified by economic changes as reflected in appropriate economic index data similar to that used under Medicare. The amended 32 CFR Part 199 would employ the Medicare Economic Index to limit the increases in prevailing charges.

DATE: Written public comments must be received on or before December 7, 1988.

ADDRESS: Send comments to the Office of Civilian Health and Medical Program of the Uniformed Services (OCHAMPUS), Office of Program Development, Aurora, CO 80045-6900.

For copies of the Federal Register containing this notice, contact the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402, (202) 783-3238.

The charge for the Federal Register is $1.50 for each issue payable by check or money order to the Superintendent of Documents.

FOR FURTHER INFORMATION CONTACT: Tariq S. Shahid, Office of Program Development, OCHAMPUS, telephone (303) 361-3587.

To obtain copies of this document, see the "*ADDRESS*" section above.

SUPPLEMENTARY INFORMATION: In FR Doc. 77-7834, appearing in the Federal Register on April 4, 1977 (42 FR 17972), the Office of the Secretary of Defense published its regulation, DoD 6010.8-R, "Implementation of the Civilian Health and Medical Program of the Uniformed Services (CHAMPUS)," as Part 199 of this title. The 32 CFR Part 199 (DoD 6010.8-R) was reissued in the Federal Register on July 1, 1986 (51 FR 24008).

I. Background

Currently, for the services of physicians and other authorized individual professional providers, the regulation provides that the allowable charge for covered care shall be the lower of: (1) The billed charge for the service; or (2) the prevailing charge level that does not exceed the amount equivalent to the 80th percentile of billed charges made for similar services in the same locality during the base period. Section 8019 of the Department of Defense Appropriation Act for Fiscal Year 1989, Pub. L. 100-463, requires that

> None of the funds contained in this Act available for the Civilian Health and Medical Program of the Uniformed Services under the provisions for section 1079(a) of title 10, United States Code, shall be available for reimbursement of any physician or other authorized individual provider of medical care in excess of the lower of: (a) the eightieth percentile of the customary charges made for similar services in the same locality where the medical care was furnished, as determined for physicians in accordance with section 1079(h) of title 10, United States Code; or (b) the allowable amounts in effect during fiscal year 1988 increased to the extent justified by economic changes as reflected in appropriate economic index data similar to that used pursuant to title XVIII of the Social Security Act.

Accordingly, beginning approximately January 1, 1989, increases in the CHAMPUS prevailing charges in effect during fiscal year 1988 for physicians and other authorized individual providers will be limited based on application of the Medicare Economic Index (MEI).

On September 29, 1988, we published in the Federal Register (53 FR 38050) a notice to defer update of CHAMPUS prevailing charge levels for professional services originally to be effective October 1, 1988. This notice specified that the deferral of the update will last for 12 months unless CHAMPUS implements the MEI method to limit growth in prevailing charges.

Effective approximately January 1, 1989, this proposed rule will implement the provisions of Pub. L. 100-463, adopting the MEI under CHAMPUS and lifting the freeze on prevailing charge levels. With the adoption of the MEI, the CHAMPUS fee screen year (the 12 month period beginning on the date the profiles are updated) will also be changed from a fiscal year to a calendar year.

II. Medicare Economic Index (MEI)

In 1972, in response to concerns about rising physician fees reimbursed under Part B of the Medicare program, Congress mandated that an additional fee limit be included in the calculation of "reasonable" charges. Under Section 224 of the Social Security Act Amendments of 1972 (Pub. L. 92-603), the prevailing charge—an amount equal to the maximum reasonable charge allowed physicians for a specific procedure in a specific locality—could exceed the July 1972-June 1973 prevailing charge only by an amount reflected by an index of changes in physicians' operating expenses and earnings levels. This index is known as the Medicare Economic Index (MEI). Under Medicare, in the case of physicians' services only, annual increases in prevailing charges are provided to account for inflation, but only to the extent that there are updates in the MEI. The MEI updates have progressively increased the initial prevailing charge level that was established for the (then) fiscal year ending June 30, 1973.

The Omnibus Budget Reconciliation Act of 1987 established the MEI for 1989 at 3.0 percent for primary care services and 1.0 percent for other services. Primary care services were defined in the accompanying Conference Report to be office medical visits, home medical visits, emergency department services, and skilled nursing, intermediate care, long-term care facility, nursing home, boarding home, domiciliary or custodial care visits.

CHAMPUS will be following the Medicare procedure in this regard, subject to changes based on differences in the CHAMPUS and Medicare programs. Under CHAMPUS, we

Coulston, A.M. and Johnson, R.K. 2002. Sugar and Sugars: Myths and realties. *Journal of the American Dietetic Association.* 102(3):351-353.

Sugar and sugars: Myths and realities

ANN M. COULSTON, MS, RD; RACHEL K. JOHNSON, PhD, MPH, RD

We all appreciate the sensation of sweetness; however, the amount of sweetened foods and beverages we eat and drink is influenced by many factors. These include age, cultural differences, economic status, health conditions, cost and availability as well as other lifestyle considerations. We cannot consider *sweetness* without mentioning *sweeteners*. Whether caloric or non-caloric, sweeteners offer the producer and consumer a choice of products to provide sweetness.

Sugars are found in foods as natural constituents such as fruits, honey and dairy products. But they are also generated during processing (cooking), added intentionally to improve the palatability of foods and beverages such as in candies and soft drinks, or used as a preservative as in jams and jellies. Sucrose, the sugar most people identify with the term "sugar" or "sweetness", occurs naturally as a component of the carbohydrate of every fruit and vegetable in the plant kingdom. It is a product of photosynthesis and occurs in greatest quantities in sugar cane and sugar beets from which it is harvested for commercial use. Sucrose is extracted from these plants through a process of water extraction, purification, filtration, concentration and drying (1). There is no difference in the sucrose from cane or beet sugar.

Chemicals that taste sweet include a variety of organic compounds, such as sugars, amino acids, peptides, proteins, and various heterocyclics. Potencies of sweeteners are conventionally compared on a weight basis with sucrose, which is given the potency of 1.0 (Figure 1). Although some of these sweeteners have a much greater potency for sweetness than sucrose, of those currently known, none possess the ideal sensory qualities of sucrose. The most important quality effects of sucrose are the temporal characteristics. These manifest as delayed reaction times to sweetness and prolonged sweet sensations. It is unclear how chemical structure affects these temporal characteristics. However, in some products, high-fructose corn syrup (HFCS) is an acceptable substitute for sucrose.

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HIGH-FRUCTOSE CORN SYRUP

The HFCS story is one of the most revolutionary in food science in the last decade. Use of HFCS has been driven partly by its price, which is well below the price of raw sugar (2). Corn refiners produce high fructose corn syrup by first converting cornstarch to syrup that is nearly all dextrose. Enzymes isomerize the dextrose to produce 42% fructose syrup called HFCS-42. By passing HFCS-42 through an ion-exchange column that retains fructose, corn refiners draw off 90% HFCS and blend it with HFCS-42 to make a third syrup, HFCS-55 (2). HFCS has a chemical structure similar to sucrose. Unlike the name—high-fructose—this sweetener is no higher in fructose than sucrose. Thus, whether sweetness comes from sucrose or HFCS, both are essentially disaccharides composed of one glucose and one fructose molecule.

Demand for HFCS is driven by the production of products that can use syrup as an ingredient. For example, 90% of HFCS-55 is used by the beverage industry. While HFCS-42 is used by the beverage industry (44%), it is also used by processed food manufacturers (21%), cereal and bakery produc-

Food Ingredient	Relative sweetness (by weight, solids)
Sucrose	1.0
Glucose	0.7
Fructose	1.3
Lactose	0.2
High Fructose Corn Syrup (42% fructose)	1.0
High Fructose Corn Syrup (55% fructose)	1.1
Aspartame	180

FIG 1. Relative Sweetness of Sugars
Adapted from: http://www.sbu.ac.uk/biology/enztech/maltose.html. Accessed: May 2, 2001.

ers (13%), the dairy industry (7%), confectionary industry (1%), and the remainder by multiple use food manufacturers (3). Supersweet HFCS-90 is used in natural and "light" products where very little volume is needed to provide sweetness. U.S. production of HFCS increased from 2.18 million tons in 1980 to 9.4 million tons in 1999 as HFCS replaced more expensively priced sugar in a variety of industrial uses. In 2000 about 5.3% of the total corn crop was used to produce HCFS (3).

SWEETENER CONSUMPTION

U.S. sweetener consumption increased by close to 8 million tons over the last twenty years to a level of about 22 million tons in 1999 (2). Sweetener consumption data include: sugar, corn sweeteners, honey, maple syrup, and other edible syrups, but exclude non-caloric sweeteners. Cane and beet sugar consumption declined in the early 1980's, as HFCS began to replace these commodities in beverages and some bakery products but began to recover and reached an estimated 9.4 million tons in 1999. Per capita consumption of caloric sweeteners increased 22% from 1970 to 1995, and has continued to increase to an estimated 158 pounds/capita in 1999.

According to U.S. Food Supply Data, Americans' per capita consumption of added sugars went from 27 teaspoons (or 108 g) per person, per day in 1970 to 32 teaspoons (or 128 g) per person, per day in 1996, an increase of 23 percent (4). This increased consumption has been driven by the dramatic increase in the supplies of corn sweeteners or HFCS (Figure 2) (4). For the purposes of analyzing the nutrient intake of Americans in nationwide surveys and in establishing the Food Guide Pyramid, added sugars are defined as all sugars used as ingredients in processed and prepared foods, such as bread, cake, soft drinks, jam, and ice cream, as well as sugars eaten separately or added to foods at the table (5).

As stated in the year 2000 *Dietary Guidelines for Americans*, consumers are advised to "Choose beverages and foods to moderate your intakes of sugars" (6). Unlike other nutrients, such as total and saturated fat and sodium, there is no guidance for the consumer as to how much sugar constitutes moderation. The only document that has received wide dissemination among the American public that offers some direction is the Food Guide Pyramid. Consumers are advised to use added sugars "sparingly" and this is defined as 6 teaspoons (or 24 g) for a 1600 kilocalorie diet, 12 teaspoons (or 48 g) for a 2200 kilocalorie diet and 18 teaspoons (or 72 g) for a 2800 kilocalorie diet (7). As the average intake of added sweeteners for the U.S. population, age two and older, is 20.5 teaspoons (or 82 g) per day (8) most Americans exceed the Food Guide Pyramid recommendations.

NUTRITION AND HEALTH CONSIDERATIONS

Misconceptions are touted for many carbohydrate-rich foods, including sucrose and HFCS. Concerns arise as epidemiological studies report an alarming increase in body weight and type 2 or "adult onset" diabetes mellitus in children and adults. Scientific studies examining the associations between carbohydrate-containing foods and beverages and the etiology of obesity and diabetes are controversial. For example, Gibson (9), and Lewis and colleagues (10) reported a negative correlation between sugar intake and body mass index. On the other hand, Ludwig and colleagues examined the relationship between consumption of sugar-sweetened beverages and childhood obesity and concluded that for every additional serving of sugar-sweetened drink consumed, the odds of becoming obese increased by 60 percent (11). Food consumption surveys reveal that over the past two decades Americans have increased their total energy intake. The increase has largely been in the form of carbohydrates, primarily in the form of soft drinks (8,12,13). Guthrie and Morton found that sugar-sweetened beverages are by far the primary source of added sugars in the diets of U.S. children (8). Others have demonstrated that children who are high consumers of soft drinks have higher energy intakes than children who are non-consumers (14) and that obese children consumer a greater proportion of their total energy intake from soft drinks in comparison with lean children (15). Finally, Keast showed that obese adults have higher soft drink intakes in comparison with lean (16).

These data are of particular concern to individuals who have the genetic propensity for insulin resistance, since excess body weight in this population almost certainly leads to carbohydrate intolerance and ultimately type 2 diabetes mellitus. Insulin resistance, which is an impaired biological response to the naturally occurring hormone insulin, is a genetic trait estimated to effect 70-80 million Americans (17). Since many older children and adults who are overweight or obese have insulin resistance, rumors abound that insulin resistance leads to obesity. This is a completely unfounded notion. People with the genetic trait of insulin resistance live a perfectly healthy life unless they overeat and markedly decrease their physical activity. There is no direct connection to carbohydrate foods, including sugar, and obesity or diabetes mellitus unless excessive consumption of sugar-containing beverages and foods leads to energy imbalance and weight gain. Sugar-containing beverages in particular have been suggested to promote obesity because compensation at subsequent meals for energy consumed in the form of a liquid could be less complete than for energy consumed in the form of solid food (18).

There is a growing view that diets very low in fat (less than 20 percent total energy from fat) and high in carbohydrate precipitate metabolic changes in the lipoprotein profile that result in atherogenic dyslipidemias (19). High carbohydrate diets, especially diets high in sugars, have been associated with increased risk of coronary heart disease (19,20)

RECOMMENDATIONS

There is no question that intakes of added sweeteners have increased dramatically in the U.S. over the past twenty years.

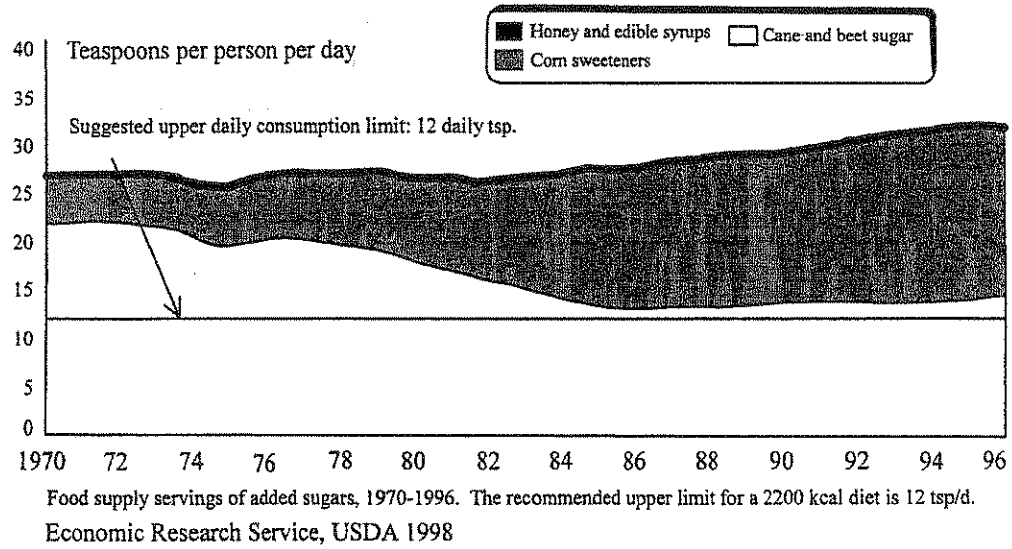

FIG 2. Added sugars: Food supply servings, 1970–96.

This has largely been attributed to increased consumption of sugar-sweetened beverages. Sugars, in the form of sucrose or HFCS, have a similar metabolic fate in the body. Growing evidence is linking excessive intakes of added sugars with undesirable health risks of obesity leading to increased incidence of type 2 diabetes mellitus and its complications, especially cardiovascular disease (21). In addition, at high levels of added sugars intakes it becomes very difficult to meet micronutrient requirements from food alone, as well as recommendations to consume the variety of foods that are needed to ensure dietary adequacy while remaining in energy balance (22). There is a role for sugars and HFCS in our food supply, but, research is teaching us that we can get too much of a good (sweet) thing.

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Manufacturing, composition, and applications of fructose[1,2]

L Mark Hanover and John S White

ABSTRACT High-fructose syrups (HFS) comprise fructose, dextrose, and minor amounts of oligosaccharides. The predominant syrups of commerce contain 42% and 55% fructose. HFS production was made possible by concurrent developments in refining, isomerization, and separation technologies in the 1960s. Fructose contributes many useful physical and functional attributes to food and beverage applications, including sweetness, flavor enhancement, humectancy, color and flavor development, freezing-point depression, and osmotic stability. HFS is used extensively in carbonated beverages, baked goods, canned fruits, jams and jellies, and dairy products. The use of crystalline fructose and crystalline fructose syrup have recently expanded from pharmaceutical and specialty food products to mainstream food and beverage applications. *Am J Clin Nutr* 1993;58(suppl): 724S–732S.

KEY WORDS Fructose, high-fructose syrup, high-fructose corn syrup, crystalline fructose, crystalline fructose syrup, manufacturing, production, composition, applications, regulatory status.

Introduction

Sweeteners have enhanced our enjoyment of food for thousands of years. Honey was the principal sweetener in the human diet until sucrose became available after the Crusades. Both honey and sucrose comprise nearly equal parts fructose and dextrose (glucose). The monosaccharides are free in honey, but linked together through a glycosidic bond in the disaccharide sucrose (**Fig 1**).

Starch is a storage polymer of dextrose in many cereals, grains, and vegetables. The discovery that starch polymers could be depolymerized to sweet monomer subunits made dextrose an attractive alternative to sucrose for some applications. However, lower relative sweetness coupled with unique physical properties and functionality left dextrose an imperfect replacement for sucrose in many food and beverage products.

Concurrent advances in refining, isomerization, and separation technologies in the 1960s made possible the production from corn starch of high-fructose syrup (HFS) with sweetness equivalent to sucrose. Ease of handling this liquid sweetener and lower price accelerated the acceptance of HFS by food and beverage producers. Today, after just 25 y on the market, HFS is consumed in amounts nearly equal to sucrose in the United States (1).

Advances in crystallization technology within the past decade led to the commercial availability of dry, crystalline fructose. This is a remarkable achievement given the poor success of producers in drying HFS, using conventional techniques.

Although sucrose from sugar beets and starch from rice, wheat, tapioca, and potato are used in the manufacture of HFS throughout the world, corn (maize) starch is by far the starch most widely used for this purpose. Its abundance and agricultural stability combine to make corn starch a low-cost raw material for the production of HFS in many countries (2).

This paper outlines the basic developments and techniques used in milling, refining, and crystallizing fructose sweeteners from corn; compares the composition and physical properties of commercially available products, and discusses their unique functional properties, uses, handling requirements, and regulatory status.

Manufacturing

The production of HFS requires the following manufacturing steps: *1*) wet milling corn to extract the starch, *2*) saccharification and liquefaction to hydrolyze polymer starch to monomer dextrose, *3*) isomerization to convert dextrose to fructose, and *4*) fractionation to enrich the concentration of fructose in the isomerization product stream. An additional step of crystallization is required for the production of dry, crystalline fructose. Unit operations comprising each manufacturing step will be discussed in detail in the sections that follow.

Corn wet milling

Corn is an abundant source of starch, as shown in **Table 1.** Starch comprises > 60% of the total weight of the corn kernel (> 70% on a dry basis). A high-molecular-weight polymer of dextrose, starch is stored in granules within the endosperm of the kernel (Fig 2), where it provides energy for the germinating seed. Starch consisting solely of straight-chain polymers of dextrose linked by α-1,4 bonds is called amylose. Amylopectin is the name given to starch polymers containing branches linked to the linear backbone via α-1,6 bonds. Corn varieties differ greatly in the ratio of amylose to amylopectin: waxy corn starch is virtually all amylopectin, normal dent corn contains nearly 30% amylose, and high-amylose corn contains 60–70% amylose. Normal dent corn is the variety most commonly used for the production of fructose syrups.

The objective of the wet-milling process is to separate starch from other corn by-products like protein, oil, and fiber. The iso-

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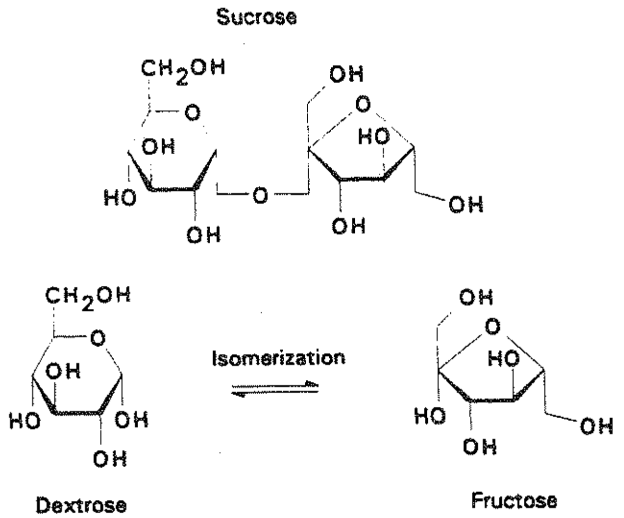

FIG 1. Chemical structures of sucrose (a disaccharide), dextrose, and fructose (monosaccharides), illustrating the conversion of dextrose to fructose by isomerization.

lated starch is a feedstock for a host of products including modified starch, dextrin, cyclodextrin, maltodextrin, corn syrup, glucose syrup, liquid and crystalline dextrose, HFS, and crystalline fructose. A typical corn wet-milling process is illustrated in **Figure 2.** The purpose of each step is briefly outlined below. For further details on the wet-milling process, *see* reference 3.

Steeping. Shelled corn is slurried (steeped) up to 4 d in warm (52 °C) water containing a low concentration of sulfur dioxide (0.01–0.02%) in preparation for milling. During this time the corn hull softens, the protein (gluten) matrix anchoring starch granules in place is denatured, and soluble sugars and nutrients in the kernel diffuse into the steep water. Sulfur dioxide is an effective protein denaturant and also functions to restrict microbiological fermentation.

Germ separation. The embryonic, oil-rich portion of the kernel is called the germ; it is the first by-product to be recovered. Steeped corn is dewatered and then passed through coarse grinding mills to break the kernel and free the germ. When broken kernels are reslurried, the loosened germ separates from the rest of the kernel because of its low relatively buoyant density. Separation is completed either with flotation tanks or hydroclone separators. Isolated germs are washed, dewatered, and dried before the oil is recovered through pressing and solvent extraction.

Fiber separation. Free fiber (corn hull) is removed from starch and gluten by using wire screens. Roughly one-third of the starch separation remains bound to the fiber however, and requires gentle buffeting in a disk mill to free it. Starch is recovered from the milled slurry by further washing and screening. The dilute fiber stream is concentrated by dewatering with screen centrifuges, screened reels, screw presses, or horizontal belt presses.

Starch separation. Protein, starch, and residual corn solubles are all that remain in the slurry after the fiber is removed. The difference in buoyant density between starch and protein is exploited to separate these two components by using "mud" centrifuges (so named because of the proteinaceous sludge that separates from the starch). Nearly 95% of the protein is recovered in this step.

TABLE 1
Yield from a typical bushel (0.04 m^3) of corn

	Proportion by weight	Weight
	%	*kg (lb)*
Starch	61.0	15.51 (34.2)
Feed	19.2	4.85 (10.7)
Oil	3.8	0.95 (2.1)
Water	16.0	4.08 (9.0)
Total	100.0	25.39 (56.0)

Washing. Starch washing is the final step in the milling process. It reduces residual impurities in the starch slurry through a series of washing and hydroclone centrifuge steps. The resultant starch slurry is of sufficient purity to serve as the starting material for fructose syrup refining.

Two important commercial by-products for the corn wet miller are corn gluten meal and gluten feed (4). Gluten meal is a high-protein, high-energy feed consisting primarily of gluten (insoluble protein) and residual amounts of starch and fiber. It also contains xanthophyll, a yellow pigment prized by poultry producers as a feed ingredient for coloring chicken. Gluten is dewatered, dried to ≈ 12% moisture, and sold in meal form. The mixture of concentrated steep water solubles and fiber is called gluten feed. It has a nutrient profile valued by cattle, poultry, and swine producers. Gluten feed is sold in dried, pelleted form.

HFS refining

The purpose of the refining process is to make functional syrup products of high purity from the starch starting material produced in the wet milling process. The refining process for HFS, illustrated in **Figure 3,** consists of acid-enzyme hydrolysis of starch, enzymatic isomerization of dextrose, chromatographic separation of isomerization products, and blending of separation streams to final product specifications. The concurrent availability of commercial-scale enzymes for isomerization, methods for immobilizing isomerase, and the development of fractionation technology to separate isomerization products made possible the pro-

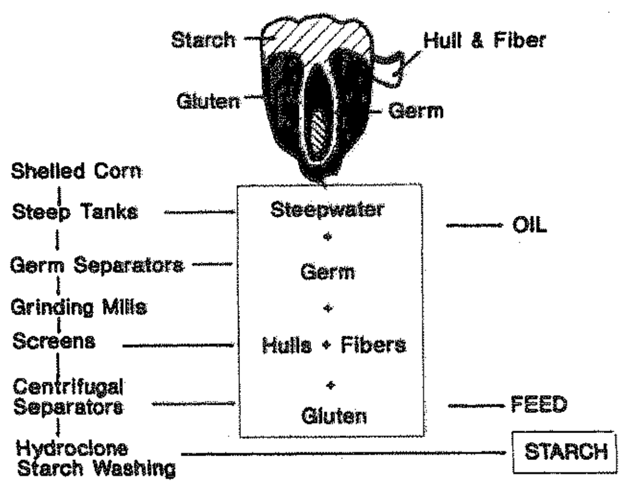

FIG 2. Cross-section of a corn kernel and typical corn wet-milling process scheme.

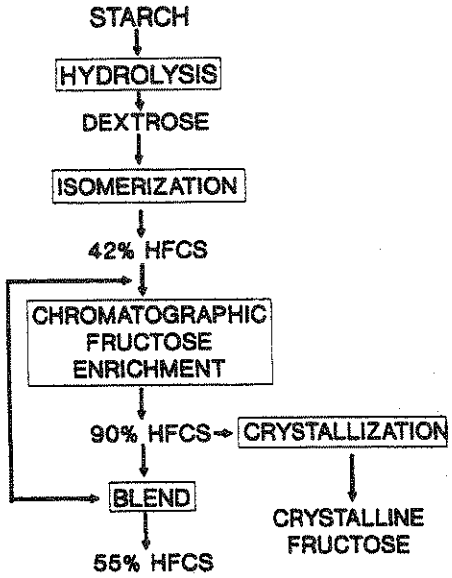

FIG 3. Typical refining process for converting corn starch to high-fructose corn syrup (HFCS) and crystalline fructose.

duction of HFS in the late 1960s. Unit processes are described below; the reader is referred to the review of HFS refining in reference (5) for further detail.

The manufacture of HFS requires the complete depolymerization of starch to its constituent monosaccharide, dextrose. Saccharification and liquefaction are names for the hydrolysis reactions used to accomplish this. Starch from wet milling is prepared for hydrolysis by a process called jetting: the starch slurry is pumped under high pressure through a small orifice with simultaneous injection of steam. This ruptures densely packed starch granules and hydrates liberated starch, permitting access to starch polymers by acid and hydrolytic enzymes.

Saccharification. Hydrolysis of the starch polymer to oligomers of intermediate molecular weight is initiated with dilute mineral acid or the enzymes α- and β-amylase. Mineral acid and α-amylase make random breaks in the starch backbone, producing soluble oligosaccharides and relatively small amounts of low- and medium-molecular-weight saccharides. Beta-amylase releases disaccharide units of dextrose (maltose) as it hydrolyzes starch.

Liquefaction. Glucoamylase completes the enzymatic hydrolysis of di- and oligomeric products of amylase by breaking the α-1,4 and α-1,6 bonds that join consecutive dextrose units. Dextrose produced by the proper combination of acid and/or enzymes exceeds 95% and provides an excellent substrate for isomerization.

Isomerization. The next major refining step in producing HFS is the isomerization of dextrose to fructose. Lobry de Bruyn and van Ekenstein (6, 7) demonstrated in 1895 that dextrose is isomerized to fructose via an enediol intermediate. Whereas alkali (eg, sodium hydroxide) will isomerize dextrose to fructose, this catalyst produces unacceptably high color and flavor with low fructose yield, and is not commercially viable. This is due in large measure to the lability of the fructose molecule and its susceptibility to degradation under these rather harsh conditions. Early attempts to enzymatically isomerize dextrose to fructose were hampered by the complex biochemical pathway linking the two sugars and the expense in regenerating essential cofactors. Akabori et al (8) discovered a glucose isomerase (actually a xylose isomerase with affinity both for dextrose and xylose) able to catalyze the conversion of dextrose to fructose without the need for cofactor regeneration. Takasaki et al (9, 10) greatly improved the economics of enzyme catalysis by immobilizing the enzyme. *Actinoplanes missouriensis, Bacillus coagulans, Flavobacterium arborescens,* and *Streptomyces* are all microbiological sources of glucose isomerase. This enzyme today remains one of the largest industrial uses for immobilization technology worldwide.

Fractionation. The amount of fructose enzymatically produced from dextrose at 60 °C, a practical processing temperature, is restricted by an equilibrium constant of ≈ 1 (11). Theoretically, the highest fructose yield possible from the 94% dextrose feed stream is 47% at equilibrium. Manufacturing plants typically settle for yields < 42% because of the amount of enzyme and reactor time required to achieve equilibrium fructose concentrations. The first immobilized isomerase reactors, in use by 1968, produced fructose yields of 42%. Trained sensory panelists judged the sweetness of this fructose syrup to be approximately nine-tenths the sweetness of sucrose at 10% solids and room temperature. HFS-42 thus became the first generation fructose syrup of commerce.

A higher fructose content was required before HFS could match the sweetness of sucrose at amounts typically used as beverage-sweetener solids. Available chromatographic separation technology using activated carbon or iron oxide gave low dextrose:fructose separation efficiencies. However, the possibility of replacing higher-priced sucrose in the lucrative carbonated-beverage industry provided tremendous economic incentive for the development of a commercially viable fructose-enrichment process. Mitsubishi Chemical Industries developed a process in which fructose is separated from dextrose and other isomerization products by virtue of its greater affinity for the calcium salt form of strong-acid, cation-exchange resin (12). The progress of fructose through the chromatography column is retarded relative to that of dextrose and the separation is accomplished. Using the Mitsubishi process and the simple blending scheme illustrated in Figure 3, Japanese and US manufacturers were producing HFS containing 55% fructose by the late 1970s. HFS-55 was adopted by the carbonated-beverage industry and became the predominant sweetener in colas by late 1984.

Fructose crystallization

The solubility of fructose at 25 °C is 4 g/per g H_2O. As shown in **Table 2**, this represents the highest solubility of most, if not all, sugars and sugar alcohols. It is for this reason that fructose is so difficult to crystallize from aqueous solution.

One patented process that was developed by T Kusch et al (13) produced a solidified crystalline mass from a concentrated (95%) solution. When cooled it formed a stable, storable anhydrous fructose. The resultant glass-like material was, however, extremely hygroscopic and deliquesced in humid conditions. Several processes were subsequently patented for the production of a fructose product in its most stable, pure crystalline form. These patents included crystallization from methanol (14), ethanol (15), and water. The US patent by Frosberg et al (16) was one of the first to describe an aqueous system.

The aqueous systems did have advantages over solvent-based systems, including lower solvent expenses and no problems with

TABLE 2
Comparison of water activity of saturated solution and solubility at 25 °C for selected crystalline sugar and polyol compounds

Crystalline compound	Water activity at 25 °C	Solubility at 25 °C
		g/g water
Mannitol	0.977	0.22
Maltose	0.952	0.85
Lactose (monohydrate)	0.931	0.23
Dextrose (monohydrate)	0.891	1.04
Sucrose	0.844	2.07
Sorbitol (gamma)	0.725	2.7
Fructose	0.634	4

TABLE 4
Typical composition of crystalline fructose and crystalline fructose syrup

	Crystalline fructose	Crystalline fructose syrup
Solids (%)	99.5	77.0
Moisture (%)	≤ 0.5	23.0
Carbohydates		
(dry solids basis)		
Fructose (%)	≥ 99.5	≥ 99.5
Dextrose (%)	≤ 0.5	≤ 0.5
Oligosaccharides (%)	Trace to none	Trace to none
Ash, sulfated (%)	≤ 0.1	≤ 0.1

residual solvent or solvent disposal. The most successful crystallization processes in use today are based on the crystallization of fructose from aqueous solution. They utilize various combinations of concentration under atmospheric or reduced-pressure conditions and seeding to initiate crystallization, followed by a cooling step to allow for crystal growth. Batch and continuous crystallization processes have been devised that incorporate preprogrammed concentrating, cooling, warming, and recooling cycles. The resultant crystals are then harvested from the crystallizers and are often washed to ensure that any traces of the saturated fructose solution are removed from the surface of the crystal. The crystals are then exposed to a further drying step to remove surface moisture before being put into bags, totes (0.9 metric tons, palletized bags), or railcars for storage and/or shipment.

Composition

Products

The primary reason for the production and ultimate consumption of fructose is its sweetness. Before the relatively recent technological advances that made the production of fructose from corn economically feasible, highly concentrated sources of fructose were limited. The major sources were honey (containing ≈50% fructose, solids basis) and a variety of invert sugar products ranging in fructose content from 20% to 50%.

Several different HFS products were initially developed in response to the needs of the soft drink market. After extensive testing and process optimization leading to improved economics, syrup containing 55% fructose was determined to be the product of choice. There is a relatively small market for very high fructose syrups—those containing 80–95% fructose. These syrups have found limited application primarily because of cost and instability. **Table 3** presents typical composition values for HFS-42, -55, -80, and -95.

Within the last 5 y a third generation of fructose sweetener, crystalline fructose, has grown significantly. It is produced in the United States from the 95% fructose fractionation product by crystallization. Elsewhere in the world, crystalline fructose is made from sucrose. The crystallization process offers advantages of a product in the dry form and very pure in fructose content, with no measurable amounts of other saccharides present. **Table 4** gives typical composition data for crystalline fructose as well as for its crystalline fructose syrup counterpart, which is produced by dissolving crystalline fructose in water.

Physical properties

HFS products are produced and sold as liquids. Values for several essential properties of these syrups are given in **Table 5.**

TABLE 3
Typical composition of high-fructose-syrup (HFS) products*

	HFS-42	HFS-55	HFS-80	HFS-95
Solids (%)	71.0	77.0	77.0	77.0
Moisture (%)	29.0	23.0	23.0	23.0
pH	4.0	3.5	3.5	3.5
Carbohydrates				
(dry solids basis)				
Fructose (%)	42	55	80	95
Dextrose (%)	53	42	18	4
Oligosaccharides (%)	5	3	2	1
Ash, sulfated (%)	0.05	0.05	0.03	0.03
Sulfur dioxide (ppm)	2	2	—	—

* Adapted from technical data sheets (AE Staley Manufacturing Co, Decatur, IL; Cargill, Minneapolis; and ADM Corn Sweeteners, Decatur, IL).

TABLE 5
Physical properties of high-fructose-syrup (HFS) products*

	HFS-42	HFS-55	HFS-90	HFS-95
Density (kg/m^3 at 37.77 °C)				
As is	1333.67	1373.21	1383.99	1385.19
Solids	946.63	1056.87	1054.47	1066.45
Refractive index (at 20 °C)	1.464	1.4786	—	—
Viscosity (Pa·s)				
27 °C	0.160	0.760	—	0.575
32 °C	0.100	0.520	—	0.360
38 °C	0.075	0.360	—	0.220
43 °C	0.052	0.240	—	—
49 °C	0.035	0.160	—	—
Color (RBU)†	≤ 25	≤ 25	≤ 25	≤ 25

* Adapted from technical data sheets (AE Staley Manufacturing Co, Decatur, IL; Cargill, Minneapolis, and ADM Corn Sweeteners, Decatur, IL).
† Reference basis units.

These products are generally described as clear or water-white. The refining processes the syrups are exposed to (carbon and ion exchange) remove most of the color in the product, as well as many trace-level compounds in the syrups that can lead to later color development. In syrups containing higher amounts of dextrose (HFS-42), the dextrose can crystallize under certain time and temperature conditions. This crystallization is reversible with the application of heat and, therefore, does not usually interfere with the final syrup application.

Crystalline fructose products are presently produced and sold in the United States in three physical forms: powdered (90% through a US 200-mesh screen) and products with an average particle size of 300 and 450 μm. The powdered product contains a flow agent, because fructose is very hygroscopic and tends to adsorb moisture from its environment, which can lead to caking or lumping problems. Crystalline fructose syrup is similar in physical properties to traditional HFS products. It has the advantages, however, of greater sweetness, purity, and improved color stability (17). Both crystalline and crystalline fructose syrup products are being introduced as key ingredients into food and beverage applications. The reasons for this, as will be discussed in the following section, go beyond the value of fructose as a sweetener.

Applications

Functional properties

Fructose and fructose-containing syrups generally exhibit multiple functional properties when used in a food or beverage product. These functional properties may be attributed either to the chemical or physical properties of the fructose itself, or to the interaction of fructose with the food or beverage system.

The primary reason that fructose is used in the formulation of food and beverage products is because of its sweetness. It is the sweetest of all naturally occurring carbohydrates. **Table 6** shows

TABLE 6
Sweetness of selected sweeteners relative to sucrose*

Sweetener	Relative sweetness
50% fructose + 50% sucrose	128
Fructose	117
Invert sugar	109
HFS-90	106
Sucrose	100
HFS-55	99
HFS-42	92
Dextrose	67
Corn syrups	
95 DE (high dextrose)	63
63 DE	45
50 DE (high maltose)	35
43 DE	34
43 DE (high maltose)	33
36 DE	30
26 DE	< 30

* Comparisons made between samples at 10% solids and room temperature relative to sucrose (relative sweetness = 100). DE, dextrose equivalents [the chemical reducing capacity relative to dextrose (DE = 100)].

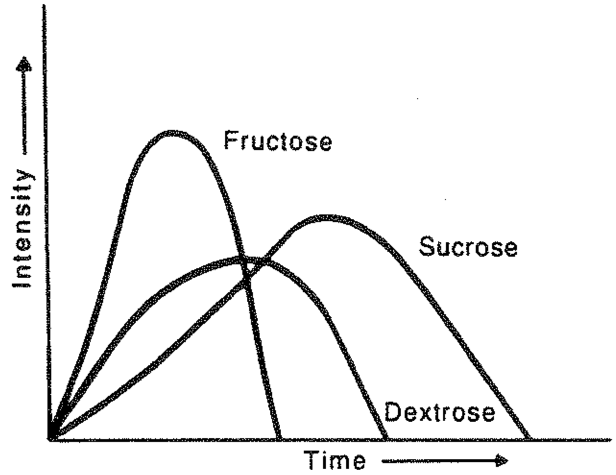

FIG 4. Comparative sweetness-intensity profiles for fructose, dextrose, and sucrose (23).

the sweetness of fructose relative to sucrose (relative sweetness) in an aqueous system at 10% dry solids and room temperature to be 117. Sucrose (table sugar) has been assigned the baseline value of 100. The positive relative sweetness of fructose-containing syrups varies according to the fructose concentration of the sweetener, because the relative sweetness of dextrose at 67 is lower than that of sucrose at 100. HFS-55, developed as a replacement for sucrose in many applications, has a relative sweetness of 99—nearly identical to sucrose.

Sweetness is system dependent, ie, the perceived sweetness in a food or beverage system depends on several factors, including temperature (18), pH, solids content, and the presence of other sweeteners. Fructose exhibits a synergy with other sweeteners present in a formulation (Table 6): the relative sweetness of a 50/50 fructose-sucrose mixture is 128 (19). Similar synergies occur when fructose is used in combination with aspartame (20), saccharin (21), and/or sucralose (22). This synergy allows a formulator to either obtain higher degrees of sweetness in the finished product without increasing the total level of sweeteners, or to retain a satisfactory degree of sweetness while reducing the amount of sweeteners used and the cost. Either way, fructose both sweetens and improves the sweetness profile.

The sweetness intensity profile of fructose is different from those of sucrose and dextrose, as shown in **Figure 4**. The sweetness of fructose is perceived earlier than that of sucrose or dextrose, and the taste sensation reaches a peak (higher than sucrose) and diminishes more quickly than sucrose. Because of this, use of fructose often results in an enhancement of other flavors in the system. Many flavors such as fruit, some spices, and acids come through more clearly and distinctly after the fructose sweetness dissipates, because they are not masked by the lingering sweetness of sucrose. Thus, fructose may improve the flavor profile and possibly even reduce costs for these flavors.

Fructose and dextrose, the major components of HFS, are both monosaccharides. Because of their colligative properties, which depend only on the concentration of particles present and not on their nature, these monosaccharides function inherently differently than does the disaccharide sucrose or the oligosaccharides in regular corn syrups. The smaller molecule of fructose, for example, creates higher osmotic pressures and lower water activities in food systems than does the disaccharide sucrose or sugars of larger molecular weights. Table 2 shows the effect on water activity of various sugars and humectants. Achieving a lower water activity allows the food formulator to achieve greater microbial stability without removing moisture that is necessary for texture and eating quality.

Table 2 also shows the solubility of fructose. Its high degree of solubility affects the control of moisture in systems in which it is used. Fructose is hygroscopic, which means it readily adsorbs water from its environment. Fructose begins to adsorb water at ≈55% relative humidity (RH), whereas sucrose adsorbs moisture in environments ≥ 65% RH. Among the advantages of fructose compared with many other sugars (eg, sucrose and dextrose) are that it will not easily crystallize when at high concentrations or lose moisture at low RHs. Fructose is an excellent humectant, meaning that it retains moisture for a long period of time even at low RH. This humectant property can be used to impart improved eating quality, better texture, and longer shelf-life to the food products in which it is used. The use of fructose with other sugars can also help control unwanted crystallization.

Another property fructose imparts, again because of its relatively small molecular weight, is depression of the freezing point of a food. Fructose (and dextrose) will lower the freezing point more than will di- or oligosaccharides. In systems in which this may be undesirable, such as soft-serve or hard-frozen dairy desserts, care must be taken to balance the formulation with sugars of higher molecular weights (eg, corn syrups) or to add the correct combinations of gums and stabilizers. In other products, however, freezing-point depression can be used to an advantage. Depressing the freezing point of frozen fruit, for example, helps protect the integrity of the fruit pieces by reducing damaging ice-crystal formation (24).

Fructose and dextrose are technically termed reducing sugars, whereas sucrose is a non-reducing sugar. The presence of reducing sugars in a formulation is important when one is trying to develop color via the classical Maillard browning reaction. Bakers depend on this reaction to give bread crust its distinctive brown color and to provide a baked color to microwaved products. The reducing property is also useful in maintaining the bright red color of tomato catsup and strawberry preserves (25). The browning reaction can be controlled to some extent by manipulation of pH and/or time and temperature of processing and storage.

Fructose provides additional functional properties to specific food systems beyond those already discussed. For example, fructose enhances starch functionality in food systems. As the curves in **Figure 5** demonstrate, fructose causes viscosity to develop more quickly and the system to achieve a higher final viscosity compared with sucrose. In products that require the starch to cook, fructose will lower the temperature required to gelatinize the starch and ultimately cause a higher final viscosity to be developed. This temperature-gelation effect was reported by White and Lauer (26) in model baking systems. Adjustments had to be made in fructose product formulas to compensate for the altered flour starch gelatinization temperature to obtain a finished product with volume comparable with that of the sucrose control.

In summary, fructose and fructose-containing syrups contribute high sweetness and flavor-enhancement properties to food and beverage products. Fructose also affects the management of moisture in the system through its humectant and osmotic pressure properties and by affecting the final water activity of the

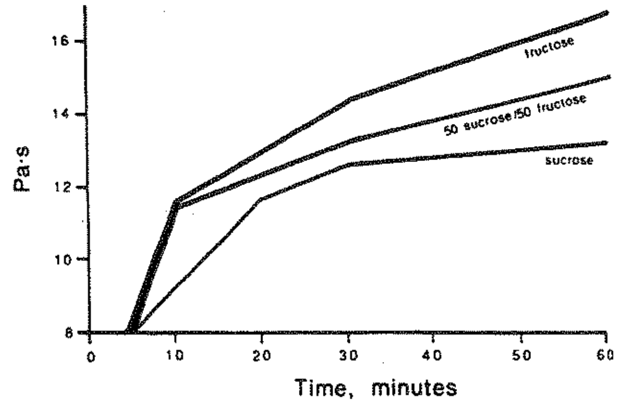

FIG 5. Viscosity of pudding prepared with STARCO 447 and various sweeteners. (STARCO is a tradename of the AE Staley Manufacturing Company, Decatur, IL, for one of its pregelatinized tapioca starches.)

product. These functional properties lead to product or process benefits for the manufacturers and consumers of food and beverages. Examples of many applications for HFS and crystalline fructose will be found in the next two sections.

HFS applications

Sucrose is a disaccharide comprising equimolar ratios of dextrose and fructose, covalently bonded together. In several major product applications of sucrose, the disaccharide is hydrolyzed to monomeric subunits through a process called inversion. Inversion is catalyzed either by the low pH of the product, as in carbonated beverages, or through the action of yeast enzymes, as in baked goods. Because the carbohydrate profile of HFS closely resembles that of an invert sugar, both of these applications became logical targets for HFS when fructose-containing syrups were first introduced.

The major applications for HFS are now carbonated beverages and raised bakery products. Bakers found that HFS gave them finished products nearly identical to those sweetened with sucrose, was more economical to use, and was easier to handle than was sucrose. Because HFS can be obtained at higher solids levels than liquid sucrose, less space is needed to store an equivalent amount of sweetener solids. HFS is also extremely resistant to microbial spoilage because of the higher solids level and the higher osmotic pressure generated by the monosaccharides. In processing plants where the possibility of airborn yeast exists, this stability was readily welcomed.

The carbonated beverage industry is the largest user of HFS-42 and -55. The 42% fructose product is used primarily in non-cola beverages, often acidified with an organic acid system that is easier to sweeten. Many cola systems, however, use phosphoric acid, which requires the higher sweetness of HFS-55 to give the correct flavor balance; alternatively, an increased amount of HFS-42 may also be used. The carbonated beverage industry was a major contributor to the improvement in quality of HFS products that has taken place in the last 10 y. The National Soft Drink Association developed stringent guidelines, complete with approved testing methodology for color, taste, odor, floc, ash, fructose, other carbohydrate amounts, and microbiological standards. These guidelines are universally employed and have served to continually improve the quality of HFS. As a result, > 90% of energy-containing carbonated beverages produced in the United States are sweetened with HFS.

Flavor enhancement and a natural compatibility with fruit flavors are two reasons the fruit-canning industry has become the third major user of HFS, behind carbonated beverages and baking industries. HFS is frequently blended with liquid sugar and corn syrups to get the right balance of sweetness and fruit flavor. Corn syrups help add eye appeal to the fruit by imparting a shiny, glossy surface appearance when the fruit is served in a dish or tray. HFS-42 is primarily used, again because of its economy and compatibility with organic acid systems.

HFS is used extensively as a sweetener in dairy products like yogurt, chocolate milk, and ice cream. Quality and economy are once more the primary reasons, in addition to improved flavor perception and rapid fermentability in yogurt, and mouthfeel and viscosity in ice cream and chocolate milk. The makers of jams, jellies, and preserves are also major users of HFS. High-solids systems can be formulated by using HFS and corn syrups without the storage problem of crystallization common to sucrose and dextrose. HFS again enhances fruit flavors and stabilizes the color in these products throughout their storage life.

Crystalline fructose applications

Applications for HFS are quite extensive and include every conceivable food and beverage product with the exception of those requiring a dry sweetener: eg, carbonated and noncarbonated beverages, baked and canned products, condiments (eg, catsup and sauces), confections, dairy products (eg, ice cream, chocolate milk, and yogurt), fruit packs (frozen), jams, jellies, preserves, meat products, pickles, reduced-energy products (HFS-95), tobacco, and wine. Crystalline fructose was introduced in 1986 by the AE Staley Manufacturing Company to meet dry-sweetener formulation needs of the food industry.

Crystalline fructose was positioned early as a nutritionally advantageous sweetener because of the way it is metabolized by the body. Therefore, many of the products first sold that contained crystalline fructose were those that went to diet or health-conscious consumers. These included various powdered diet beverages and meal supplements, nutritional candy bars, and other specialty food items. These applications were successful in introducing fructose to many consumers, but crystalline fructose was not considered to be an ingredient for mainstream food products primarily because of its high cost relative to sugar and dextrose. The development of the technology for crystallization of fructose from HFS-90 led to the commercialization of fructose on a larger scale and at a lower cost than was previously possible.

Application areas for crystalline fructose now include dry mix beverages, for which the intense sweetness of fructose allows for a reduction in total sweetener content and a parallel reduction in energy. Energy reduction, simple-sugar reduction, and flavor profile enhancement are three popular formulation trends that fructose can favorably impact. Other applications that capitalize on the sweetener synergy to reduce energy include "lite" pancake syrups and "lite" carbonated beverages. The use of crystalline fructose and sucrose in these products can reduce the energy value by at least one-third, qualifying it for a reduced-energy label. Other application areas include breakfast cereals (flavor enhancement, sweetness synergy); yogurt, chocolate milk, and egg nog (flavor enhancement, energy reduction); baked goods (humectancy, starch synergy, flavor enhancement); fruit packs (flavor enhancement, storage stability); energy supplement in sports drinks (solubility, flavor enhancement, sweetness); and confections (sweetness, starch synergy, humectancy). Crystalline fructose and crystalline fructose syrup add a new dimension to food and beverage product development that can allow formulators to improve their existing products, formulate new product concepts, improve their manufacturing processes, and/or reduce costs.

Handling requirements

HFS

HFS can be stored and handled in most corn syrup or liquid sugar systems. Stainless steel, milled steel coated with a non-reactive material, or combinations of these materials may be used for tanks and pipes, whereas steel and cast iron are suitable for accessory valves, meters, fittings, and pumping equipment. Aluminum may be used for pipes and fittings but is not recommended for tank shells.

It is recommended that HFS-42 be stored within a temperature range of 35–41 °C. At temperatures < 35 °C, the possibility of dextrose crystallization becomes much greater. Although this crystallization is reversible with the application of heat, it does present a processing problem that can be time-consuming to resolve, especially if the location is not equipped or if there is insufficient time to rectify it. At temperatures > 41 °C HFS will increase in color, going from water white to straw yellow or darker. HFS-55 can be stored at lower temperatures, 24–29 °C, because the possibility of dextrose crystallization is much less because of the reduced concentration of dextrose in the product. Once again, color development can occur at temperatures > 29 °C.

As previously discussed, the high osmotic pressure exerted by the monosaccharides and high solids in HFS help prevent microbial spoilage. In fact, whereas HFS-42 is bacteriostatic, HFS-55 is bactericidal. To ensure stability in storage, however, it is rec-

TABLE 7
Food Chemicals Codex requirements for high-fructose syrup (HFS)*

Description. "High fructose [corn] syrup is a sweet, nutritive saccharide mixture prepared as a clear aqueous solution from high dextrose equivalent [corn] starch hydrolysate by the partial enzymatic conversion of glucose (dextrose) to fructose, using an insoluble glucose isomerase preparation complying with 21CFR 184.1372 that has been grown in a pure culture fermentation that produces no antibiotics. It a water-white to light-yellow, somewhat viscous liquid that darkens at high temperatures. It is miscible in all proportions with water."

Assay. "Not less than 97% total saccharides, expressed as a percent of solids, of which not less than 51% nor more than 55% consists of glucose, and not more than 7% consists of other saccharides."

Arsenic (as As)	Not more than 1 mg/kg.
Color	Within the range specified by the vendor.
Heavy metals (Pb)	Not more than 5 mg/kg.
Lead	Not more than 0.5 mg/kg.
Residue on ignition	Not more than 0.05%.
Total solids	Not less than 70%.
Sulfur dioxide	Not more than 0.003%.

* Adapted from requirements for high-fructose corn syrup (HFS) in references (29, 30).

TABLE 8
Food Chemicals Codex requirements for crystalline fructose*

Description. "Fructose occurs as white, hygroscopic, odorless, purified crystals or as a purified crystalline powder having a sweet taste. It is a natural constituent of fruit (hence, the name "fruit sugar") and is obtained from glucose in corn syrup by the end use of glucose isomerase. Its density is about 1.6. It is soluble in methanol and in ethanol, freely soluble in water and insoluble in ether."

Assay. "Not less than 98.0% and not more than 102.0% fructose ($C_6H_{12}O_6$), after drying."

Arsenic (as As)	Not more than 1 ppm.
Chloride	Not more than 0.018%.
Glucose	Not more than 0.5%.
Heavy metals (as Pb)	Not more than 5 mg/kg.
Hydroxymethylfurfural	Not more than 0.1%, calculated on the dried basis.
Lead	Not more than 0.1 mg/kg.
Loss on drying	Not more than 0.5%.
Residue on ignition	Not more than 0.5%.
Sulfate	Not more than 0.025%.

* Adapted from references (30 and 31).

ommended that storage tanks be equipped with a combination surface blower unit and ultraviolet (UV) light. The blower unit will keep the surface of the syrup from becoming diluted by condensation running down off the top of the tank. Condensation can dilute the solids level of the top few inches of the HFS low enough to allow microbial spoilage to occur, particularly from yeast and mold. UV light adds extra insurance to minimize risk of microbial contamination at the surface.

Crystalline fructose and crystalline fructose syrup

The most important factor in storing and handling crystalline fructose is the RH. It is recommended that bulk handling of crystalline fructose be done only in conditioned air systems with an RH of ≤ 55% and a maximum temperature of 24 °C. These conditions are being successfully applied to handle bulk fructose from railcars and throughout customers' plants. Bagged fructose should be stored under similar conditions to prevent subsequent caking and flow problems with the product. Most bagged fructose is presently being packed in foil-lined paper bags to ensure minimal transfer of moisture to the product. Crystalline fructose syrup can be stored under similar conditions to those for HFS-55. The recommended storage temperature for crystalline fructose syrup is 21–29 °C. Crystalline fructose syrup can be held without any fear of crystallization and is very stable microbially as well.

Regulatory status

Fructose in one form or another is obviously used in food supplies worldwide. Few countries, if any, have taken specific steps to approve or otherwise regulate various fructose-containing food ingredients by law or implementing regulation. HFS, crystalline fructose, and other fructose-containing ingredients have simply been considered, like sucrose, to be de facto generally recognized as safe (GRAS).

HFS

In the United States, HFSs are affirmed by regulation as GRAS for their current uses. In 1988 the Food and Drug Administration proposed to recognize the long history of safety for fructose and reaffirm the GRAS status of HFS as a direct human food ingredient (27). The petition is specific for HFS-42, but may include HFS-55 on review of its additional processing steps. For further information, see reference 28. Food Chemicals Codex requirements for high fructose corn syrup are listed in **Table 7** (29, 30).

Crystalline fructose

The Food Chemicals Codex (30, 31) and United States Pharmacopeia (32) define fructose as containing not less than 98% or more than 102% fructose (on the basis of analytical variance), and not more than 0.5% glucose. This definition is met only by crystalline fructose and crystalline fructose syrup. Food Chemicals Codex requirements for crystalline fructose are listed in **Table 8.** The Codex Alimentarius Commission describes fructose as "purified and crystallized D-α-fructose" (33). These requirements are met only by crystalline fructose.

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Highs and Lows of High Fructose Corn Syrup

A Report From the Center for Food and Nutrition Policy and Its Ceres® Workshop

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Since the early 1980s, the prevalence of overweight/obesity in the US population, as well as per capita consumption of high fructose corn syrup (HFCS), has increased. Although some public health researchers and administrators hypothesize that these 2 trends are directly related, current research published in the scientific literature does not support a cause-effect relationship between HFCS consumption and overweight/obesity rates. Some explanations for the popularity of these unsupported hypotheses may be due to confusion concerning the compositional differences, or lack thereof, between HFCS, sucrose, and other sweeteners. In addition, failure among individuals in the scientific community to distinguish between HFCS and "corn syrup" may exacerbate the confusion. Before any relationship between HFCS consumption and overweight/obesity can be examined, more information concerning current levels of HFCS in the food supply, as well as individual-level HFCS consumption, must be established.

The prevalence of overweight/obesity in the US population has steadily increased since the early 1980s.[1,2] Presently, about 64% of all Americans are overweight, with more than 30% of these individuals classified as obese. Children and adolescents also are increasingly overweight. About 15% of the US population aged 6 to 19 years are currently overweight, almost double the rate of the past two decades.[3] A recent assessment estimated that obesity-related morbidity accounts for approximately 9.4% of total healthcare expenditures in the United States.[4]

Due to increased public awareness of the US obesity "epidemic," the scientific community, government agencies, and politicians have focused their attention on determining the causes of and solutions to this relatively recent and pervasive trend. Although many hypotheses have been proposed, including the venerable "energy balance" explanation, an increasingly popular approach is to blame a specific food or food ingredient for the rise in overweight/obesity in the US population. However, this clearly is an oversimplification because there are many variables that contribute to obesity. During the same period that Americans were becoming increasingly overweight/obese, the proportion of high fructose corn syrup (HFCS) consumed as part of the American diet was also increasing. In 1970–1974, the per capita annual average HFCS consumption was only 1.5 pounds,* with consumption gradually increasing to 27.4 pounds* in 1980–1984. By 2000, the per capita annual average HFCS consumption in the United States was 62.7 pounds.* During the same period, sucrose (refined cane and beet sugar) consumption decreased from 100.5 to 65.6 pounds.*[5] According to USDA's Economic Research Service, however, the daily average intake of HFCS has declined in the United States since reaching record-level highs in 1999.[6] Because the proliferation of HFCS in the US food supply roughly follows the rising overweight/obesity trend in the population, some researchers hypothesize that HFCS has played a significant role in America's overweight/obesity epidemic.[7–9]

Manufacturing Breakthroughs in the 1970s Led to Greater Use of HFCS

Until the late 1970s, most food products manufactured in the United States were sweetened with sucrose. Due

*Pounds, dry-weight equivalent; based on aggregate data; unadjusted for spoilage, plate waste, and other losses.

to advances in the HFCS production process, HFCS has replaced sucrose in many food products. Corn is easily and widely grown in the United States. Corn starch, composed of 2 types of glucose polymers (amylose and amylopectin), has been successfully isolated from corn and converted to glucose and glucose-containing products for nearly a century. However, the process of converting glucose to its sweeter isomer—fructose—previously involved an alkaline isomerization process that resulted in an unacceptable product for use in foods. In addition to causing flavor and color problems in the final food products, the alkaline isomerization process was economically unviable due to low yields. In 1970, a new enzymatic process using xylose isomerase efficiently produced HFCS-42, a sweetener derived from corn starch that contains about 42% fructose and has acceptable flavor and color profiles. In addition, HFCS-42 is almost as sweet as sucrose. Further developments in the late 1970s using a fructose enrichment system with a strong-acid, cation-exchange resin resulted in the commercial availability of HFCS-55, which contains about 55% fructose and has the same sweetness as sucrose.

Sucrose is a disaccharide composed of one glucose and one fructose molecule bonded together. Food scientists have known for many years that the bond between glucose and fructose is subject to hydrolysis at low pH and moderate temperatures—those typically encountered, for example, in a carbonated beverage prior to retail sale. Hydrolyzing this bond can cause sweetness, texture, and viscosity changes in a food or beverage, and the development of unacceptable flavor. HFCS became a more enticing sweetener option for food manufacturers once flavor, color, and yield issues were resolved. HFCS is not subject to hydrolysis because its glucose and fructose molecules are present in the "free," or monosaccharide, state. This property makes HFCS a very stable product for use in many beverage and food applications. HFCS-42 is used primarily in foods such as baked goods, canned fruit, dairy products, jams, jellies, and preserves; HFCS-55, on the other hand, sweetens many beverages including carbonated soft drinks, sports drinks, teas, and fruit-flavored ades.

Compositions of HFCS, Sucrose, Invert Sugars, and Honey Are Similar

Much confusion concerning the different types of sweeteners exists within the scientific community and the general public. Because of its name, HFCS is incorrectly assumed to be much higher in fructose than most other sweeteners. A component comparison of HFCS-42,

Extrapolating results from studies using pure fructose and applying those results to HFCS is inappropriate.

sucrose, HFCS-55, invert sugar, and honey is shown in Table 1.

The fructose/glucose ratio of HFCS-42 is slightly lower than the 50:50 ratio found in sucrose, whereas HFCS-55 has a slightly higher fructose/glucose ratio than sucrose. In fact, all of the listed sweeteners are relatively similar in percent fructose and glucose composition. The main difference between these sweeteners is the percent moisture content of sucrose (solid form) compared with the other 4 sweeteners (syrup-based).

At this time, there is no scientific evidence to suggest that humans utilize either HFCS-42 or HFCS-55 any differently than sucrose, invert sugar, or honey. All disaccharides are completely hydrolyzed in the gastrointestinal tract into their simple sugar (monosaccharide) components prior to absorption. In order to hydrolyze sucrose into fructose and glucose, the small intestine secretes an enzyme known as sucrase, which is abundant and not rate-limiting. Consequently, the rate of absorption for the monosaccharide components of sucrose and HFCS is likely to be equal in both speed and completeness.

Fructose and glucose are absorbed and metabolized differently by the human body.[10,11] However, fructose is fructose and glucose is glucose regardless of the

Component (%)	HFCS-42	Sucrose	HFCS-55	Invert Sugar	Honey
Fructose	42	50	55	45	49
Glucose	53	50	42	45	43
Others	5	0	3	10	8
Moisture	29	5	23	25	18

source—HFCS, sucrose, invert sugar, or honey. In other words, after hydrolysis in the gut, the monosaccharides derived from these sweeteners are physiologically indistinguishable to the human body.

Glucose is actively absorbed in the duodenum via a sodium-dependent hexose transporter (SGLUT-1). After glucose passes into the bloodstream, insulin is released by the pancreas to facilitate its absorption by the cells. Fructose is passively absorbed further down the small intestine in the lower duodenum and jejunum. Following absorption, fructose enters the bloodstream but does not stimulate the release of insulin.[12] Both fructose and glucose must be converted to pyruvate, through a process known as glycolysis, before entering the Citric Acid Cycle.[13] The various metabolic pathways of fructose and glucose and the intermediary metabolism of each monosaccharide in the liver and other tissues have been thoroughly documented in the scientific literature.[11,14,15]

Inaccurate Terminology Confuses Scientists and the Public Alike

Despite the compositional similarities between HFCS, sucrose, invert sugar, and honey, some articles published in the scientific literature imply that the human body processes HFCS differently from other sweeteners. Moreover, inaccurate terminology in the literature promotes confusion and misinformation. Gross et al[7] conducted an ecological correlation study examining the relationship between dietary fat, carbohydrate, protein, fiber, corn syrup, and total energy consumption and the prevalence of Type 2 diabetes in the United States between 1909 and 1997. Using a multivariate nutrient-density model and after controlling for total energy, the authors concluded that the prevalence of Type 2 diabetes was negatively associated with fiber consumption ($P < .01$) and positively associated with corn syrup consumption ($P = .038$). In this study, the authors evaluated corn syrup as an indicator of all refined carbohydrates because corn syrup is "a highly refined substance that is consumed in vast quantities in the United States in the form of soft drinks, commercial baked goods, ready-to-eat breakfast cereals, and many other commercially processed food products."

It is unfortunate that Gross uses the term "corn syrup" to refer to "high-fructose corn syrup." These food products are compositionally different, and the 2 terms should not be used interchangeably. Using incorrect terminology further increases the confusion surrounding HFCS within the scientific community and the general public.

Although a positive association was found between "corn syrup" consumption and the prevalence of Type 2 diabetes, this does not imply a causal relationship. Type 2 diabetes has been consistently linked to obesity, not to consumption of sweeteners. Consumption of calories beyond the amount needed by the body is directly related to obesity. All macronutrients, not just sweeteners, contain calories and can contribute to obesity when consumed in excess.

A recent study by Bray et al[8] suggests that consumption of beverages containing HFCS may be a factor in the overweight/obesity epidemic. The authors hypothesize that beverages containing HFCS are "sweeter" than beverages containing sucrose, and cravings for the sweeter beverages have led to overconsumption. According to Hanover and White,[16] however, the relative sweetness levels of HFCS-42 and HFCS-55 are 92 and 99, respectively, compared with sucrose (set at 100). The *iso-sweet* (same sweetness) levels of sucrose and HFCS-55 have been confirmed by expert sensory panels.

More Research Is Needed to Determine Levels of HFCS in the Food Supply

Currently, there is no convincing evidence to support a link between HFCS consumption and overweight/obesity. Moreover, overweight/obesity is a worldwide health problem even in countries and regions that do not use HFCS. The escalating rate of overweight/obesity coincides with many more credible explanations than increased HFCS consumption.

There is also no evidence to suggest that humans absorb or metabolize HFCS any differently than sucrose. Moreover, a study conducted by McDevitt and associates[17] showed no differences among lean and obese women in 96-hour energy or macronutrient balance in response to overfeeding of fructose, glucose, sucrose, or fat. Some scientists hypothesize that dietary fructose has increased over the last several years, which has coincided with increases in overweight and obesity. Research therefore should be directed at determining how much HFCS there currently is in the food supply and whether or not this has led to an increase in overall fructose consumption. Obtaining this information would contribute to better analyses of any possible relationship

Currently, there is no convincing evidence to support a link between HFCS consumption and overweight/obesity.

between overweight/obesity and HFCS consumption. In addition, human studies need to directly evaluate HFCS. Results from experiments testing pure fructose and applying those results to HFCS are inappropriate because fructose and HFCS are compositionally different.

Not only is it imperative that the appropriate corrective measures be taken to reduce the incidence of overweight/obesity, it is also critical to avoid squandering valuable resources pursuing unlikely theories based on questionable use of data. Promoting untested hypotheses confuses and frustrates the general public and fosters ineffective policy solutions that detract from other more effective and efficient solutions. In addition, great restraint and care should be exercised by scientists and communicators, including the media, to avoid confusing the public further.

Afterword

This report is an excerpt of the presentations and discussions from the Ceres® Workshop on the *Highs and Lows of High Fructose Corn Syrup* that was convened on May 10, 2004. This 1-day workshop was organized by the Center for Food and Nutrition Policy, Virginia Tech—National Capital Region and cosponsored by the Joint Institute for Food Safety and Applied Nutrition, University of Maryland. The workshop included presentations by Dr. John S. White, President of White Technical Research, who addressed the manufacture, composition, and functionality of HFCS. Dr. Marilyn Schorin, President of Focus Nutrition, LLC, reviewed the literature. Dr. Richard Forshee, Director of Research at the Center for Food and Nutrition Policy, focused on the applicability of the USDA's Continuing Survey of Food Intake by Individuals (CSFII) and the National Center for Health Statistics' National Health and Nutrition Examination Survey (NHANES) in HFCS consumption studies. Finally, Dr. G. Harvey Anderson, Professor of Nutritional Sciences and Physiology at the University of Toronto, discussed studies involving biological reactions to HFCS in humans.

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High Fructose Corn Syrups, Part 1

Composition, Consumption, and Metabolism

Marilyn D. Schorin, PhD, RD, FADA

High fructose corn syrup, as used in foods, is similar in composition and sweetness to sucrose. Absorption and metabolism of HFCS is also similar to that of sucrose. Although introduced into the food supply in 1968, popularity of HFCS as a sweetener grew after the Food and Drug Administration's 1983 decision that HFCS is Generally Recognized as Safe (GRAS). Part 1 of this article explains the composition, consumption patterns, and metabolism of HFCS. Part 2 explores the health impact of HFCS consumption.

Historically, most soft drinks were sweetened with sucrose. The advent of enzymatically modified corn syrup, which is less costly than sucrose yet similar in taste, led to its adoption as the principal sweetener in carbonated beverages in the early 1980s. Today, high fructose corn syrup (known by the initials HFCS) is used in a range of food products, from baked goods and energy bars to candy and carbonated and noncarbonated drinks.

Developed in the late 1960s, HFCS was created by advances in enzyme technology that allowed conversion of corn starch to corn syrup and then to fructose.[1] Working closely with food manufacturers, syrup producers refined HFCS in the 1970s to replicate the sensory properties of sucrose, which resulted in a product containing 45% glucose (and glucose polymers) and 55% fructose,[2,3] referred to as HFCS 55.

HFCS was Generally Recognized as Safe (GRAS) by the Food and Drug Administration (FDA) in 1983.[4,5] Its GRAS status was reaffirmed in 1996[6] in the Code of Federal Regulations (21CFR 184.1866).

HFCS is similar to sucrose (table sugar), the principal disaccharide of human diets around the world; both consist of glucose and fructose.

Recently, some scientists and journalists, attempting to account for the epidemic rise in obesity, principally in the United States, have focused attention on the increased use of HFCS. This 2-part article examines the salient scientific facts about HFCS, as distinct from pure fructose and other sugars, to evaluate whether there are health concerns specific to HFCS consumption. Part 1 reviews the composition, consumption, and metabolism of HFCS. Part 2 reviews research relating to obesity, appetite, glycemic control, and hyperlipidemia.

Similarity of High Fructose Corn Syrup to Sucrose

What is high fructose corn syrup? HFCS is similar to sucrose (table sugar), the principal disaccharide of human diets around the world, in that both sweeteners are composed of the monosaccharides glucose and fructose. In the sucrose molecule, these monosaccharides are held together with a glycosidic bond as a disaccharide, sucrose, that is enzymatically cleaved in the small intestine to yield one molecule each of fructose and glucose. HFCS does not require enzymatic hydrolysis in the small intestine, because it is composed almost entirely of the monosaccharides, glucose and fructose. These monosaccharide molecules of HFCS are absorbed in the duodenum and upper jejunum. Glucose is absorbed by an energy-dependent process requiring sodium transport. Fructose absorption involves a sodium-independent transporter GLUT-5.

Although sucrose is a disaccharide, it hydrolyzes to its monosaccharide components in acid media (such as in most sweetened carbonated beverages and lemonade). The extent of hydrolysis is dependent on time, temperature, and pH.[7] By the time they are consumed, many sucrose-sweetened carbonated beverages may, in fact, contain significant amounts of free glucose and fructose and, therefore, closely resemble HFCS in this respect. [Note: The older literature often refers to hydrolysis of sucrose as "inversion" and the product, an equimolar mixture of glucose and fructose, is referred to as "invert sugar." The term "invert" originates from and its bypass of the critical regulatory step in glycolysis of phosphofructokinase. In addition, although fructose does not directly cause insulin secretion, insulin is secreted when fructose is consumed in combination with glucose. In type 2 diabetes, fructose ingestion stimulates insulin secretion; the clinical significance of this effect is unclear.[23] Fructose ingestion has been reported to be associated with hyperlipidemia, but the clinical relevance is uncertain as a number of studies reporting such results were conducted with supra-physiological concentrations of fructose.[8]

Summary

High fructose corn syrup of the type commonly found in the food supply is similar in composition and sweetness to sucrose. HFCS was introduced into the food supply in 1968, and it gained rapid acceptance by both the food industry and consumers from 1980 onwards. Consumption of HFCS has stabilized since the late 1990s. HFCS is absorbed and metabolized in a manner similar to sucrose.

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High Fructose Corn Syrups, Part 2

Health Effects

Marilyn D. Schorin, PhD, RD, FADA

High fructose corn syrup use in food gradually increased from its introduction in 1980 until the late 1990s. The monosaccharide components of high fructose corn syrup and sucrose are identical. Part 2 of this article explores the health effects of high fructose corn syrup, including obesity, type 2 diabetes, blood lipids, and dental caries. Nutr Today. 2006;41(2):70-77

Sweet foods and beverages have traditionally been part of Western dietary patterns. The Old Testament refers to "the land of milk and honey" to convey sweetness and comfort. Enjoyment of sweets is inborn and so ingrained in us that even infants respond positively when tasting something sweet. But nutrition professionals are wondering if the recent shift in sweetener use in the United States from sucrose to high fructose corn syrup (HFCS) has specific good or ill health effects.

High fructose corn syrup is similar in composition and sweetness to sucrose (table sugar). It is absorbed and metabolized like sucrose. Introduced into the food supply in 1968, HFCS gained rapid acceptance by both the food industry and consumers after 1980. Consumption of HFCS has stabilized since the late 1990s. This article reviews research relating the health effects of HFCS to obesity, appetite, glycemic control, and hyperlipidemia. The term health effects is used, rather than adverse effects, because consumption of HFCS includes some beneficial characteristics; for example, sugars provide energy that may be essential in some diets.

Effect of HFCS on Body Weight

The incidence of obesity in the United States and, indeed, in the entire world has increased dramatically since the mid-1970s.[1,2] Scientists and policymakers have struggled to find the reason for its dramatic and unprecedented rise. Although it is well understood that obesity results from the imbalance between energy consumed and energy expended in activity, other social, cultural, behavioral, and genetic factors have also been implicated.[3-6] A decline in energy-demanding manual labor, increases in television viewing and computer use, expanded use of the automobile, the suburbanization of the population, lifestyle changes associated with women in the work force, and genetically determined "fat hormones" are all implicated in obesity.

Recently, some researchers have suggested that the switch from sucrose to HFCS is a factor in the obesity epidemic. One argument is that HFCS became prevalent in the mid-1970s, and by the mid-1980s, Americans were consuming more corn sweetener (although *not* more HFCS) than sucrose. Bray[7] drew a parallel between increases in the use of HFCS and obesity incidence, citing data on HFCS disappearance of 1 lb per person in 1970, when HFCS was introduced, to approximately 60 lb today and the prevalence of obesity jumping from 10% to 15% of the population 35 years ago to 26% today. The difference between "disappearance" and true consumption data was discussed in Part 1 of this series.

From 1970 to 2003, sucrose consumption decreased by more than one third. Thus, the primary questions are (1) whether the increases in obesity and HFCS availability are simply coincident with no causal components or (2) whether HFCS has *unique* properties that might induce overconsumption or metabolic abnormalities.

It is important to note that association does not imply causation. Causation is just 1 of 3 possible relationships between 2 correlated variables. The association of events may be caused by a common response; that is, both variable X and variable Y change in common to some third, unaccounted for variable. For example, ice cream sales and shark attacks both increase during summer. This is not because sharks start attacking in response to ice cream but because the 2 variables exhibit a common response to the warm season. The association of events may also be confounding; that is, the effect of variable X and variable Y is entangled with the effects of other explanatory variables on Y and it is not possible to separate the contribution of any single causal factor to the observed effect. For example, as cola consumption increased in recent years, there has been a corresponding decrease in the consumption of milk. However, a number of confounding factors make it impossible to assign causation to this associate. For example, there has been an increased recognition that milk contains undesirable saturated fat and that milk may cause dyspepsia in lactase-deficient individuals. To date, there are no studies that demonstrate definitively and unambiguously the causality between HFCS consumption and obesity. Causality is very definitive and indicates that a change in one event always leads to a change in the second. Because so many concomitant factors changed between the mid-1970s and 2003, it is scientifically unjustifiable to blame one commodity for a problem like obesity, which is multifactorial.

It is unlikely that a single commodity is responsible for the obesity epidemic.

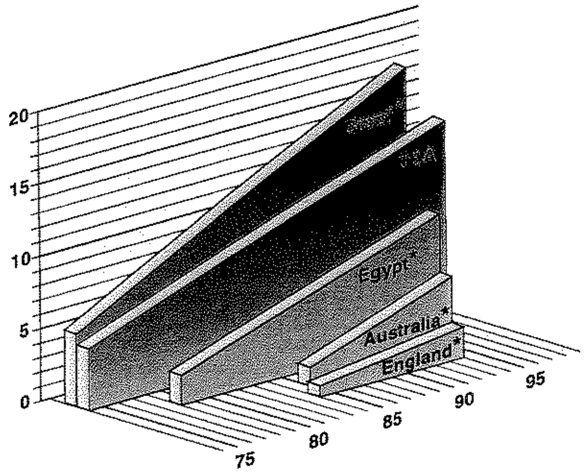

Figure 1. Increased prevalence of childhood obesity. *Countries *not* using HFCS.

The lack of causality between HFCS consumption and obesity is evident when the prevalence of obesity in the United States is compared with that of other countries where HFCS use is limited.[8] For example, the prevalence of childhood overweight has increased more than 2-fold in England in 10 years, almost 4-fold in Egypt in 18 years, and 3.4- to 4.6-fold in Australia in 10 years.[9] In these countries, food and beverages are still largely sweetened with sucrose and HFCS is not a common sweetener. Across the globe, there is a dramatic increase in obesity, independent of HFCS use (Figure 1).

Although epidemiologic evidence does not support a unique effect of HFCS on obesity, questions have been raised on whether there is an association between HFCS consumption and energy intake. Indirect data have come from studies using sucrose, a caloric sweetener that is chemically, closely related to HFCS.

For example, a 10-week study of Raben et al[10] showed that overweight men and women, consuming relatively large quantities of sucrose (28% of energy), primarily in beverages, exhibited increased energy intake, body weight, fat, and blood pressure, compared with those who consumed artificial sweetener. In a 3-week study of normal-weight individuals, Tordoff and Alleva[11] investigated whether aspartame or HFCS consumed in beverages significantly affected food intake and body weight. Energy intake and body weight increased only in subjects consuming HFCS, and the authors concluded that calorically sweetened beverages can lead to overconsumption of calories and, therefore, to overweight. However, it is worth noting that in blinding the participants to beverage composition, the investigators removed the normally present cognitive component that enables eaters to compensate for beverage calories by controlling their food and beverage intake. Thus, these data may not be relevant to real-life eating situations.

In contrast, Saris[12] reviewed evidence from carefully controlled laboratory studies, clinical trials, studies in populations at high risk of developing obesity, and epidemiologic studies on the role of sugars, particularly sucrose. He concluded that sugar intake by itself is not associated with weight gain. In fact, the CARMEN study demonstrated that individuals lost more weight when carbohydrates, including simple sugars, replaced fat in their diets.[13] High-sucrose diets produced as great a weight loss as low-sucrose diets (HFCS was not included in these studies), with no adverse metabolic or emotional effects.[14]

Furthermore, several reports indicate that carbohydrate and sugar consumption is associated with lower body mass index.[3,15,16] However, in these studies, physical activity was not held constant and the sugar type was not considered independently. An extensive analysis of US Department of Agriculture's 1994–1996 Continuing Survey of Food Intake by Individuals for the Institute of Medicine National Academy of Sciences noted that sugar consumption had no effect on body weight, although it also noted that when added sugar in the diet exceeded 25% of total energy, micronutrient intake was inadequate.[3] A similar conclusion was reached by the United Nations' Food and Agriculture Organization. In their extensive review of carbohydrate nutrition, it was concluded that despite metabolic differences in the types of carbohydrate, there was no differential effect on body weight. For the prevention of obesity, the Food and Agriculture Organization reaffirmed its commitment to a low-fat, high-carbohydrate diet.[17] The 2003 World Health Organization report on Diet, Nutrition, and Chronic Disease, however, recommended a limitation on "free sugar" (a term used by the World Health Organization that is similar to "added sugar") to 10% of energy intake as a goal for the prevention of diet-related chronic diseases.[8] The rationale for this recommendation is that "free sugars" contribute to the overall energy density of the diet and promote positive energy balance.

Although body weight and body mass index result from the balance between energy intake and expenditure, some studies have examined intake of sugars, particularly in soft drinks, and drew conclusions on obesity, without accounting for energy expenditure. For example, Harnack et al[18] found that preschool children who consumed more than 9 oz soft drinks per day (11.5% of the population) had higher energy intakes than the 88.5% who consumed less soft drink. Among school-aged children, the 32% consuming more than 9 oz soft drinks had higher energy intakes than the other 68%. However, these authors' conclusion that this contributes to childhood obesity cannot be substantiated, as they did not correlate consumption either with obesity or energy expenditure.

By contrast, in the National Health and Nutrition Examination Survey,[19] there was no correlation between regular (ie, sweetened) soft drink consumption and body weight in children.

Ludwig et al[20] analyzed data from the Planet Health project in 548 ethnically diverse 11-year-old school children in Massachusetts. They reported that the risk of becoming obese increased by 60% for each additional serving of sugar-sweetened drink that the children consumed. Note that the study showed that soft drink consumption above the baseline—not each soft drink itself—increased the risk of obesity in these children. The Ludwig et al[20] study did not report other aspects of dietary intake. The investigators acknowledged that the study was observational in nature and, therefore, could not demonstrate causality, nor did it have sufficient statistical power. Nonetheless, these findings have been widely interpreted that soft drink consumption causes obesity.

The article of Havel[21] on signaling mechanisms that influence energy intake postulated that dietary fructose can lead to overeating and weight gain as a result of decreased levels of circulating insulin and leptin. These 2 hormones, when increased, prompt a decrease in energy intake. However, it is inappropriate to equate HFCS with pure fructose because the effect of fructose will be modulated by the almost equimolar presence of glucose, which promotes increased secretion of insulin and leptin. To date, no studies have directly linked HFCS with leptin levels.

High Fructose Corn Syrup and Appetite

Several reports examined the putative relationship between sugar and appetite, but no studies specifically looked at the role of HFCS itself. A recent review[22] of sugar and satiety concluded that sugars stimulate satiety mechanisms and reduce food intake. When subjects were not informed whether they were getting a sugar-sweetened or diet beverage, they did not alter food consumption to account for beverage calories.[10] Because many people specifically select a diet beverage to control their energy intake, failure to adjust their intakes could be attributed to cognitive factors, equal satiety, or both.

> ***HFCS does not create a unique effect on appetite or subsequent food intake.***

At least 1 study suggests that liquids are less satiating than solids. DiMeglio and Mattes[23] found that jelly beans, but not soft drinks, subsequently reduced food intake, and thus, did not increase body weight. The specific sweeteners used in these experiments were not identified; thus, it is not known whether HFCS was used or if it exerted a specific effect in that study. A recent review of the satiating quality of liquid versus solids, but not necessarily HFCS liquids, highlighted the variable influence of subject selection.[24] Almiron-Roig and Drewnowski[25] compared food intake after consumption of cola, unsweetened orange juice, low-fat milk, and sparkling water. The first 3 beverages are of equal caloric density but have different sweeteners, that is, HFCS in cola, sucrose and fructose in orange juice, and lactose in milk. Despite the product differences, these investigators found that food intake was lower after the consumption of caloric beverages compared with water, but there was no difference in intake or ratings of hunger among the cola, juice, or milk drinks. Therefore, this study suggested that HFCS does not create a unique effect on appetite or subsequent food intake compared with other sweeteners.

High Fructose Corn Syrup and Dental Caries

The are no data relating HFCS and dental caries. However, it is well established that the cariogenic effect of food, presumably including HFCS, depends on multiple factors, including composition of the total diet, frequency of consumption of the food, stickiness, and how long the food remains in the mouth. For example, soft drinks have a high content of fermentable carbohydrates (such as sucrose, glucose, and fructose) but have less cariogenic effect when consumed rapidly rather than sucking a hard candy for an extended time. Consuming soft drink with a meal further reduces the cariogenic potential of HFCS-containing beverage because other food properties such as fiber, fat, and minerals interfere with the drink's effect on tooth decay. Most experts on oral health counsel that the consumption of any food, including HFCS, should be accompanied by good oral hygiene practices—frequent brushing with a fluoride-containing dentifrice, regular flossing, and routine dental visits.

Glycemic Control and Type 2 Diabetes

Historically, recommendations for diabetes management included restriction in sugar intake because the disease was characterized by increased blood glucose and the presence of glucose in the urine. (The term "diabetes" throughout this article refers to type 2 diabetes.)

Today, diabetes and nutrition experts confirm that sucrose and starch have similar effects on elevating blood glucose. For example, when sucrose is substituted for a variety of starches—in meals or snacks, both acutely and for up to 6 weeks—the glycemic response (see below) is similar if the total amount of carbohydrate is similar (see Franz MJ. Carbohydrate and diabetes: is the source or the amount of more importance? *Curr Diab Rep.* 2001;1(2):177–186). Experts also agree that sucrose and sucrose-containing foods need not be restricted in patients with diabetes to control blood sugar level, although sugars must be counted as part of the total carbohydrate intake.[26] Expert recommendations did not separately consider the effects of HFCS, most likely because HFCS is metabolized like sucrose.

Some nutrition experts have proposed the glycemic index (GI) to determine the quantitative effect of food on blood glucose levels. The GI is a ranking of carbohydrates based on their immediate effect on blood sugar (blood glucose) levels. The GI is measured as the area under the curve for the increase in blood glucose observed after the ingestion of a set amount of carbohydrate in a food during the postprandial period. This is compared with the blood glucose response from a reference food (white bread or glucose) tested in the same individual under the same conditions. The GI concept has been expanded to include the "glycemic load," which takes into account total carbohydrate intake. It is calculated by multiplying the weighted mean of the dietary GI by the percentage of total energy from carbohydrate.

The GI has been determined for a number of foods and carbohydrate-containing ingredients. The GI of HFCS is similar to that of sucrose.[27] Tables listing the GI of foods do not always specify whether the foods and beverages were made with HFCS or sucrose. For example, European and Australian soft drinks are typically made with sucrose. However, given the similarity in composition, there is likely little difference in GI. High fructose corn syrup and sucrose have equivalent effects on plasma glucose and insulin.[28] Plasma glucose levels are greater after HFCS ingestion compared with pure fructose[29] in non–insulin-dependent diabetic subjects. Fructose, unlike glucose, is widely recognized as lacking an insulin-stimulating effect.

A recent study compared the metabolic effects of a high-carbohydrate, low-fat diet that contained either 10% or 40% of total carbohydrate as fructose in children.[30] No significant differences in plasma glucose, triglycerides, insulin, C-peptide, or insulin sensitivity were found between the 2 regimens; the short-term changes in fat and carbohydrate intake, regardless of fructose content, did not affect any of the measured parameters.

The glycemic index and glycemic load have also been studied.

This contrasts with a study in rats which found that fructose was the nutrient mediator of sucrose-induced insulin resistance and glucose intolerance.[31] However, because the animals were given up to 34% calories from fructose, the findings may not be clinically meaningful.

We already observed that many researchers confuse fructose and HFCS although the 2 compounds are not the same. Elliott et al[32] referred to an increase in HFCS consumption since 1970, which they then linked to increased plasma lipids, energy intake, and weight gain; however, the evidence was based on studies of fructose, not HFCS. They ignored the fact that overall fructose consumption during this period remained almost constant. High fructose corn syrup has been a variable in only a few metabolic studies of both rodents and humans; far more have been conducted with pure fructose.

Rats exhibited insulin resistance and hyperinsulinemia after 2 weeks following a high fructose (60% of energy), but not a high-glucose, diet.[33] Both lean and obese rats showed insulin abnormalities. In lean rats, glucose, but not fructose, resulted in increases in both fat pad and body weight. However, such nonphysiological quantities of dietary monosaccharides raise questions about the relevance of such studies to typical human diets.

Investigators for the Women's Health Study analyzed sugar intake, including glucose, fructose, sucrose, and lactose, from food frequency questionnaires of more than 39,000 subjects. Intake was compared with incidence of non–insulin-dependent diabetes mellitus. No association was found between type 2 diabetes and intake of any of these sugars, affirming the American Diabetes Association's guideline that moderate amounts of sugar can be incorporated into a healthy diet.[34,35] However, a more recent epidemiologic study showed an association between consumption of sugar-sweetened beverages, weight gain, and the incidence of type 2 diabetes in women.[36] It should be noted that these types of studies represent a retrospective statistical analysis. The data cannot indicate a cause and effect relationship and may represent a lifestyle epiphenomenon or other confounding factors. Further research is required to determine whether this connection applies to all sugar-sweetened foods.

Effect of High Fructose Corn Syrup on Blood Lipids

Many investigators who have tried to understand the health consequences of HFCS have focused on the unique metabolic properties of fructose, a component of both sucrose and HFCS.

Fructose is absorbed from the intestine into the portal system and is taken up by the liver. There, it enters into the glycolytic pathway (Figure 2A) or, alternatively, gluconeogenesis (Figure 2B) as triose phosphate, bypassing the rate-limiting phosphofructokinase regulatory step that is used in the glycolytic breakdown of glucose. When fructose is consumed as a monosaccharide, it is largely converted to glucose and stored as glycogen in the liver or is released into the circulation as glucose.

Note, however, that fructose derived from sucrose or HFCS is accompanied by an almost equal amount of glucose, causing an increased release of insulin. Elevated levels of insulin inhibit gluconeogenesis. Therefore, the major fates of fructose contained in sucrose or HFCS is the production of energy or, to a lesser extent, storage as lipid (Figure 2A).

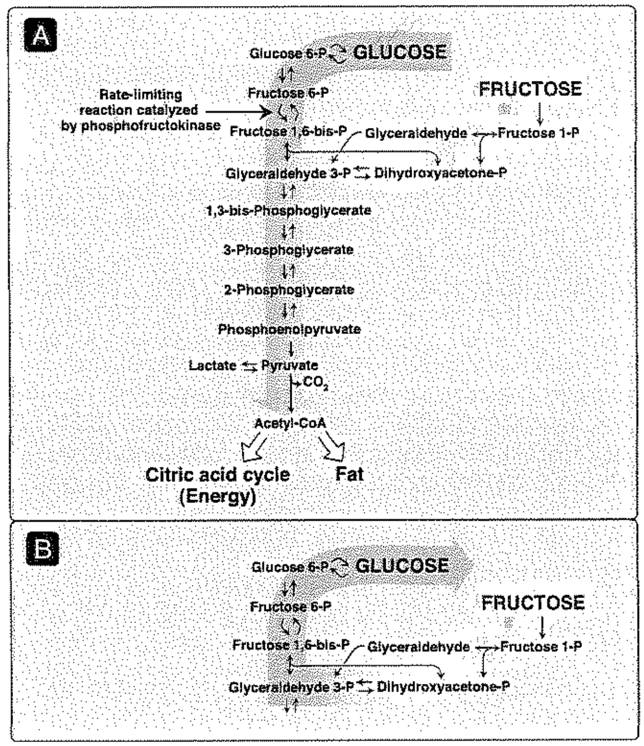

Figure 2. Metabolism of glucose and fructose. A, Glycolysis. B, Gluconeogenesis.

High intakes of fructose can stimulate lipogenesis in the liver. In addition, the triglyceride response to fructose may be different than the response to fructose-plus-glucose. Bantle et al[37] showed that 6 weeks of a very high fructose diet (17% of total energy) versus a high-glucose diet (14% of total energy) increased serum triacylglycerol concentrations (but it had no effect on daylong plasma glucose concentrations). In the US diet, in contrast, approximately 7% to 9% of energy intake is derived from fructose. About one third of the fructose intake comes from fruits, vegetables, and other natural sources, and two thirds from additions to food and beverages (soft drinks, candies, jams, syrups, bakery products, etc).[38]

Mayes,[39] on the other hand, did not observe an increase in lipogenesis in perfused rat livers in the presence of physiological concentrations of fructose alone. However, when glucose and fructose were infused together, there was a marked uptake of glucose and an increase in glycogen. The 2002 Dietary Reference Intakes report cites mixed effects of dietary sucrose, glucose, or fructose on serum triglycerides from numerous studies. Nonetheless, numerous studies in rodents document an increase in plasma triglycerides from fructose feeding, albeit at supraphysiological doses of fructose. Although several earlier studies reported an effect of fructose on de novo lipogenesis in humans,[40] a recent review indicated that de novo lipogenesis is not a quantitatively major pathway in normal adults on typical Western diets.[41]

Few studies have examined the effects of HFCS itself on plasma lipids. Therefore, it is often necessary to infer effects from the metabolism of glucose plus fructose. There is a well-characterized hypertriglyceridemic effect of a high-carbohydrate, low-fat diet.[37,42,43] This effect is generally attributed primarily to fructose; glucose has less of a triglyceride-raising role.[43] One study, however, found no differences in blood triglycerides based on the use of sucrose, fructose, or xylitol, although plasma cholesterol was lower in the fructose group.[44]

Factors contributing to the hypertriglyceridemic effect of carbohydrates include not only the type and amount of monosaccharides but also many others.[45] In one study, a switch from a high-fat, low-carbohydrate diet to a low-fat, high-carbohydrate diet was made gradually, and the rise in triglycerides was avoided.[46]

High Fructose Corn Syrup and Cancer

Although some forms of cancer are related to diet, no studies have shown a link between HFCS itself and cancer. Cancer incidence and mortality generally increased between 1975 and 1990 but stabilized or decreased in the 1990s.[47] Investigators have examined the association of various sugars in specific cancer sites. Pancreatic cancer incidence showed no relationship to dietary carbohydrate or sucrose.[48] The fructose transporter GLUT5 was found to be increased in breast cancer cells compared with normal breast cells, but investigators did not examine whether there was any association with diet.[49] An increased risk of colorectal cancer due to sugar added to coffee or hot beverages was observed in a study in Northern Italy,[50] but the observation was not further investigated in relation to total diet or other dietary components. Another study found reduced risk of prostate cancer with greater fructose intake.[51] Thus, the picture with respect to cancer and carbohydrate intake is still unclear and needs further investigation.

Summary

The intake of HFCS has increased since 1980, when it was first introduced into the US food supply, and has been stable since the late 1990s, although obesity rates have continued to climb. The monosaccharide components of HFCS and sucrose (glucose and fructose) are identical molecules, and few studies have shown a metabolic difference between them. Given what we know about the metabolism of orally ingested sugars, it is difficult to identify a plausible physiological explanation for how approximately equal amounts of fructose and glucose should have differential effects when chemically bonded (such as in sucrose) or not (such as in HFCS). Thus, the current evidence does not support claims of a specific unique effect of HFCS on health. There has been little research specifically related to the association of HFCS with obesity or other chronic diseases. In addition, it should be noted that in many European countries where there have been increases in the prevalence of obesity over the past several decades, the rise in HFCS consumption has been trivial.

Acknowledgment

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Link Between Midlife Obesity and Higher Risk of Hospitalization, Death

Middle-aged individuals without high blood pressure or high cholesterol levels, but who are obese, have an increased risk in older age for hospitalization or death from coronary heart disease, cardiovascular disease, or diabetes, compared to individuals of normal weight, according to a study in *JAMA*.

Lijing L. Yan, PhD, MPH, of the Feinberg School of Medicine, Northwestern University, Chicago, and colleagues examined the relationship of body mass index (BMI) earlier in life with illness and death outcomes in older age (ie, 65 years and older), among individuals without and with other major risk factors at baseline. The Chicago Heart Association Detection Project in Industry study included 17,643 men and women aged 31 through 64 years, who were free of CHD, diabetes, or major electrocardiographic abnormalities at baseline (1967-1973). Cardiovascular risk was classified as low: systolic blood pressure 120 or less and diastolic blood pressure 80 mm Hg or less, serum total cholesterol level less than 200 mg/dL, and not currently smoking; moderate risk: nonsmoking and systolic blood pressure 121-139 mm Hg, diastolic blood pressure 81-89 mm Hg, and/or total cholesterol level 200-239 mg/dL; or having any 1, any 2, or all 3 of the following risk factors: blood pressure 140 or greater/90 mm Hg, total cholesterol level 240 mg/dL or greater, and current cigarette smoking. Body mass index was classified as normal weight (18.5-24.9), overweight (25.0-29.9), or obese (30 or greater). Average follow-up was 32 years. In multivariable analyses that included adjustment for systolic blood pressure and total cholesterol level, the researchers found that the risk for CHD death for obese participants, compared with those of normal weight in the same risk category, was 43% higher for the low-risk group and nearly 2.1 times higher for the moderate-risk group. Compared to those of normal weight, obese individuals in the low-risk group had a 4.2 times higher risk for CHD hospitalization; for the moderate-risk obese group, the risk of CHD hospitalization was twice as high. Results were similar for other risk groups and for cardiovascular disease, but stronger for diabetes (low risk, 11 times increased risk for death and 7.8 times increased risk for hospitalization).

The researchers suggest that their findings and other studies provide strong support for population-wide, multifaceted, primary prevention starting at young age of all major risk factors, including overweight and obesity, as a key element for the national effort to continue the progress already achieved toward ending the epidemic of CHD and CVD.

Source: *JAMA.* 2006;295:190-198.

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Straight talk about high-fructose corn syrup: what it is and what it ain't[1–4]

John S White

ABSTRACT

High-fructose corn syrup (HFCS) is a fructose-glucose liquid sweetener alternative to sucrose (common table sugar) first introduced to the food and beverage industry in the 1970s. It is not meaningfully different in composition or metabolism from other fructose-glucose sweeteners like sucrose, honey, and fruit juice concentrates. HFCS was widely embraced by food formulators, and its use grew between the mid-1970s and mid-1990s, principally as a replacement for sucrose. This was primarily because of its sweetness comparable with that of sucrose, improved stability and functionality, and ease of use. Although HFCS use today is nearly equivalent to sucrose use in the United States, we live in a decidedly sucrose-sweetened world: >90% of the nutritive sweetener used worldwide is sucrose. Here I review the history, composition, availability, and characteristics of HFCS in a factual manner to clarify common misunderstandings that have been a source of confusion to health professionals and the general public alike. In particular, I evaluate the strength of the popular hypothesis that HFCS is uniquely responsible for obesity. Although examples of pure fructose causing metabolic upset at high concentrations abound, especially when fed as the sole carbohydrate source, there is no evidence that the common fructose-glucose sweeteners do the same. Thus, studies using extreme carbohydrate diets may be useful for probing biochemical pathways, but they have no relevance to the human diet or to current consumption. I conclude that the HFCS-obesity hypothesis is supported neither in the United States nor worldwide. *Am J Clin Nutr* 2008;88(suppl):000S–000S.

INTRODUCTION

High-fructose corn syrup (HFCS) is a liquid sweetener alternative to sucrose (table sugar) used in many foods and beverages. Early developmental work was carried out in the 1950s and 1960s, with shipments of the first commercial HFCS product to the food industry occurring in the late 1960s. Phenomenal growth over the ensuing 35 or more years made HFCS one of the most successful food ingredients in modern history (1).

HFCS was used in relative obscurity for many years. After all, its compositional similarity to sucrose suggested that it would be metabolized in a like manner. Its safety was never seriously doubted because expert scientific panels in every decade since the 1960s drew the same conclusion: sucrose, fructose, glucose, and, latterly, HFCS did not pose a significant health risk, with the single exception of promoting dental caries (2–5).

Although there was considerable speculation in the 1980s that fructose was responsible for several metabolic anomalies (6–8), convincing proof that this was a significant health risk was never forthcoming. It came as a great surprise to many when, seemingly overnight, HFCS was transformed from a mundane ingredient into the principal focus of scientists, journalists, and consumers concerned about the growing incidence of obesity in the United States and around the world. This article will probe the basis and implications for the current hypothesis that HFCS is somehow uniquely responsible for rising obesity rates and will challenge the science purported to demonstrate a unique role for HFCS in promoting obesity.

BRIEF HISTORY OF HIGH-FRUCTOSE CORN SYRUP

Sucrose from sugar cane or sugar beets has been a part of the human diet for centuries; sucrose from fruit or honey has been a part of the human diet for millennia. Sucrose continues to be the benchmark against which other sweeteners are measured. However, sucrose has posed significant technological problems in certain applications: it hydrolyzes in acidic systems (9), changing the sweetness and flavor characteristics of the product, and it is a granular ingredient that must be dissolved in water before use in many applications. Furthermore, sugar cane was traditionally grown in equatorial regions, some known equally well for both political and climatic instability. The availability and price of sugar fluctuated wildly in response to upsets in either one. AQ: 1

HFCS immediately proved itself an attractive alternative to sucrose in liquid applications because it is stable in acidic foods and beverages. Because it is a syrup, HFCS can be pumped from delivery vehicles to storage and mixing tanks, requiring only simple dilution before use. As an ingredient derived from corn—a dependable, renewable, and abundant agricultural raw material of the US Midwest—HFCS has remained immune from the price and availability extremes of sucrose. It was principally for these reasons that HFCS was so readily accepted by the food industry and enjoyed such spectacular growth.

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[2] Presented at the American Society for Nutrition Public Information Committee symposium "High Fructose Corn Syrup (HFCS): Everything You Wanted to Know, But Were Afraid to Ask," held at Experimental Biology 2007 in Washington, DC, 30 April 2007.

[3] Preparation of this article supported by the American Society for Nutrition.

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TABLE 1
Carbohydrate composition of common nutritive sweeteners[1]

Component	HFCS-42	HFCS-55	Corn syrup	Fructose	Sucrose	Invert sugar[2]	Honey
	%	%	%	%	%	%	%
Fructose	42	55	0	100	50	45	49
Glucose	53	42	100	100	50	45	43
Others	5[3]	3[3]	100	0	0	10[4]	5[5]
Moisture	29	23	20	5	5	25	18

[1] From references 21, 32, and 33. HFCS, high-fructose corn syrup.
[2] Sucrose-based sweetener in which the bond between glucose and fructose is partially or fully hydrolyzed (inverted) by acid or enzyme (invertase).
[3] Readily hydrolyzable polymers of glucose.
[4] Unhydrolyzed sucrose.
[5] Sucrose and minor amounts of other carbohydrates.

THE HYPOTHESIS

In 2004 Bray et al (10) published the hypothesis that HFCS is a direct causative factor for obesity. They based their hypothesis on a temporal relation between HFCS use and obesity rates between 1960 and 2000.

Although the HFCS-obesity hypothesis may have been initially developed, as Popkin recently claimed, to simply "spur science" (11), it quickly took on a life of its own. This once mundane ingredient became vilified in scientific circles and then in the public arena when the hypothesis was translated as fact through leading nutrition journals, weekly and specialty magazines, national and local newspapers, and an endless number of television news programs.

In attempting to make sense of the HFCS-obesity hypothesis, it is fair to expect several inherent assumptions to hold true before it can be accepted as fact:

- HFCS and sucrose must be significantly different,
- HFCS must be uniquely obesity-promoting,
- HFCS must be predictive of US obesity,
- HFCS must be predictive of global obesity, and
- Eliminating HFCS from the food supply must significantly reduce obesity.

Here I examine each assumption to see whether it holds true.

HIGH-FRUCTOSE CORN SYRUP AND SUCROSE ARE NOT SIGNIFICANTLY DIFFERENT

Composition

Confusion about the composition of HFCS abounds in the literature. The carbohydrate compositions of the most common
T1 nutritive sweeteners are listed in **Table 1** (12, 13). The 2 most important HFCS products of commerce contain 42% fructose (HFCS-42) and 55% fructose (HFCS-55). The remaining carbohydrates in HFCS are free glucose and minor amounts of bound glucose, predominantly maltose (di-glucose) and maltotriose (tri-glucose). Mention of HFCS with higher fructose content (ie, HFCS-80 or HFCS-90) is occasionally seen in the literature, but these products are highly specialized and are manufactured infrequently and in insignificant amounts.

Gross et al (13) and others have confused HFCS with common corn syrup, but as shown in Table 1, they are clearly distinct products. Corn syrup is actually a family of ingredients made up only of glucose—either free or bonded to itself in chains of various lengths up to ≈10, depending on the specific corn syrup product.

HFCS is also frequently confused with pure fructose, probably because of its name. "High-fructose corn syrup" is, in retrospect, an unfortunate choice of name, because it conjures up images of a product with very high fructose content. The original intent of the name was simply to distinguish it from ordinary, glucose-containing corn syrup. Pure crystalline fructose has been available to the food industry since the late 1980s, but is still used in relatively minor amounts. The obvious differences between HFCS and pure fructose are aptly demonstrated in Table 1: the latter contains no glucose and is a low-moisture crystalline material. It must be emphasized that from a composition standpoint, pure fructose is a poor model for HFCS.

The glucose-to-fructose ratio in HFCS is nearly 1:1; similar to the ratio in sucrose, invert sugar, and honey. A similar ratio is also found in many fruits and fruit juices. The only practical distinction in composition between sucrose and other fructose-containing sweeteners is the presence of a bond linking fructose and glucose (sucrose chemical name: β-d-fructofuranosyl-α-d-glucopyranoside; 14). The glucose and fructose in HFCS, invert sugar, honey, and fruit is principally monosaccharide (free, unbonded). Thus, when HFCS historically replaced sucrose in formulations, no increase in dietary fructose occurred.

Invert sugar is the name given to sucrose in which the bond linking fructose and glucose has been hydrolyzed. This may be accomplished either with acid or enzyme (invertase). Acid-catalyzed inversion of sucrose is accelerated by increased temperature and reduced pH and takes place within time spans as short as minutes to as long as months (9). Because carbonated beverages are low in pH (colas are near pH 3.5) and are stored in warehouses at ambient temperature—sometimes for weeks before they reach supermarket shelves—considerable inversion can take place before the product reaches the consumer. It is a sweet irony that purists who must have their sucrose-sweetened sodas end up drinking a sweetener composition more similar to HFCS and have been doing so since the first cola was formulated in the 1880s.

Availability

The HFCS-obesity hypothesis of Bray et al relies heavily on the positive association between increasing HFCS use and obesity rates in the United States (10). However, Bray et al treated this association in isolation, offering no perspective on trends in AQ: 2
total caloric intake or added sweeteners use in comparison with

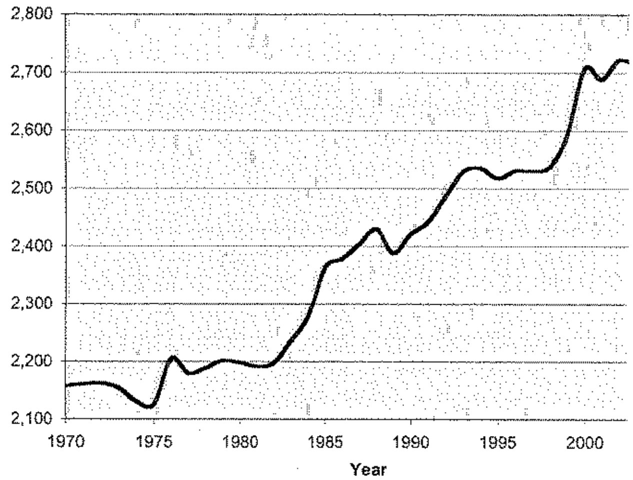

FIGURE 1. Per capita daily caloric intake (US Department of Agriculture Economic Research Service loss-adjusted availability), 1970–2005 (15).

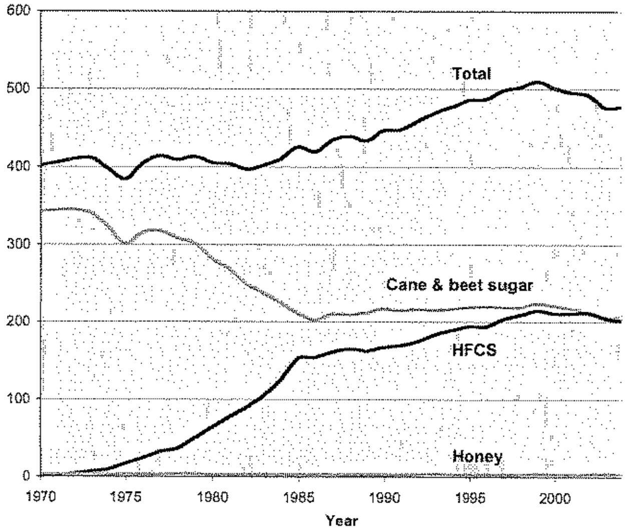

FIGURE 3. Per capita daily caloric intake of fructose-containing sweeteners (US Department of Agriculture Economic Research Service loss-adjusted availability), 1970–2005 (15).

use of other dietary macronutrients. Loss-adjusted food availability data from the US Department of Agriculture Economic Research Service to provide that missing perspective are com-
F1-2 pared in **Figures 1** and **2** (15). Availability data attempt to provide
AQ: 3 a more realistic estimate of the amount of food actually available for consumption by subtracting losses in manufacturing, transportation, food preparation, spoilage, and table wastage from food production figures.

Plotted in Figure 1 are per capita daily calories over the 35-y period from 1970 to 2005, the most recent data available. As has been widely reported, per capita daily calorie intake increased 24% over that time period.

Trends in caloric intake of major dietary nutrients over the same period are illustrated in Figure 2 to determine whether added sugars increased disproportionately, which is something they surely would have had to do to uniquely impact obesity. In fact, use of added sugars as a fraction of daily calorie intake actually decreased slightly, along with vegetables, dairy, and

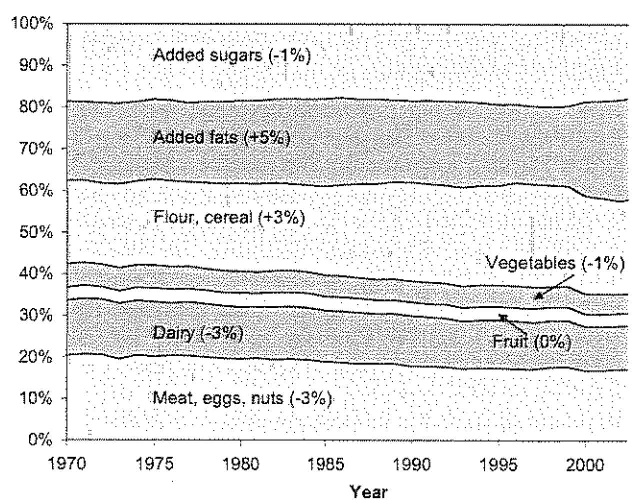

FIGURE 2. Change in percentage of daily caloric intake of nutrient groups (US Department of Agriculture Economic Research Service loss-adjusted availability), 1970–2005 (15). Numbers in parentheses indicate percentage change over the time period relative to change in total calories.

meat, eggs, and nuts. It is significant that added fat was up 5%, because evidence is growing that added fat is more strongly associated with obesity than are added sugars (16).

It is widely believed that HFCS eclipsed sucrose long ago as the primary nutritive sweetener in the US diet and that fructose concentrations have risen disproportionately as a result, but this is just not so. Per capita daily calories from cane and beet sugar, HFCS, honey, and their total are plotted over the past 35 y in
Figure 3. The following points are important to note: F3

- There was essentially a one-for-one replacement of sucrose with HFCS from 1970 to 1998;
- Since 1998, sucrose use and HFCS use have been roughly equivalent, a significant fact that has escaped too many writers on the subject;
- Fructose contributes ≈200–250 kcal/d (sucrose and HFCS are each half fructose), ≈7–8% of the current 2700-kcal/d per capita total calorie intake reported in Figure 1;
- Honey use is slight in comparison with the other 2 and has remained largely unchanged; and
- Although availability of sugars was up over this period, which confirms the data shown in Figure 2, use of added sweeteners as a percent of total calories has declined in recent years.

Two additional facts are worthy of note here: *1*) although commercially available, pure crystalline fructose remains a specialty sweetener used in very limited quantities, and *2*) the ratio of fructose-to-glucose from added sugars is ≈0.7, and this value has likely remained unchanged since sucrose use became widespread a century ago (17).

Sweetness

A common misconception about HFCS is that it is sweeter than sucrose and that this increased sweetness contributed to the obesity crisis by encouraging excessive caloric food and beverage consumption (10). HFCS is not sweeter than sucrose. The sweetness of several common nutritive sugars in crystalline and liquid or syrup form is compared in **Table 2**. T2

TABLE 2
Sweetness comparison for selected nutritive sweeteners[1]

Sugars	Sweetness intensity (crystalline)[2]	Relative sweetness (10% syrup)[3]	Absolute sweetness (syrups)[4]
Fructose	180	117	—
Sucrose	100	100	100
HFCS-55	—	99	97
Glucose	74–82	65	—

[1] HFCS, high-fructose corn syrup.
[2] Adapted from Schallenberger and Acree (18).
[3] Adapted from White and Parke (21).
[4] Calculated from Schiffman et al (20).

Sweetness intensities of crystalline compounds were reported in pioneering work by Schallenberger and Acree in 1971 (18). They determined that fructose in the crystalline, β-d-fructopyranose anomeric form has ≈1.8 times the sweetness of crystalline sucrose; the relative sweetness of crystalline glucose is lower at 0.7–0.8. Note that the sweetness of HFCS cannot be determined in crystalline form because HFCS does not crystallize. It is this marked difference in sweetness between fructose and sucrose in crystalline samples that is often confused and inappropriately attributed to HFCS, a blend of equal amounts of glucose and fructose in liquid or syrup form.

Once in solution, β-d-fructopyranose undergoes rapid mutarotation to give a mixture of several tautomers with lower and differing sweetness intensities (19, 20). White and Parke (21) reported the sweetness values of liquid and syrup samples relative to the sucrose standard as established by trained, expert food industry taste panels. In syrup form at 10% solids (the approximate sweetener concentration in most carbonated beverages), HFCS-55 and sucrose yield the same relative sweetness. Under the same experimental conditions, HFCS-42 is less sweet than sucrose, with a value of ≈0.9.

In 2000 Schiffman et al (20) reported the absolute sweetness of syrups at various concentrations and temperatures. The HFCS absolute sweetness value reported in Table 2 was calculated by regressing Schiffman's data for fructose and glucose to 10% solids and then substituting the resulting values into the known compositions of HFCS-55 and sucrose. Using sucrose once again as the standard by setting its sweetness equal to 100, a sweetness value of 97 was calculated for HFCS-55, providing independent validation for the value reported by White and Parke. Schiffman's work also confirmed the earlier work of Hyvonen et al (22) and White (23) that temperature has little effect on sweetness intensity.

These data confirm what the food industry has claimed for more than 20 y: the sweetness intensities of HFCS-55 and sucrose are equivalent. The replacement of sucrose by HFCS-55 did not change the sweetness intensity of foods and beverages, nor did it lead to a "sweetening of America" (24).

Caloric value

HFCS and sucrose are both carbohydrate ingredients that contribute ≈4 kcal/g on a dry solids basis. There can be no argument that long-term overconsumption of foods and beverages containing either one without compensation for energy expenditure may lead to weight gain.

Absorption and metabolism

All fructose-containing nutritive sweeteners appear to share the same intestinal sites for absorption. Honey, fruit sugars, and HFCS reach the small intestines predominantly as monosaccharides. The minor amount of polysaccharide glucose in HFCS is quickly broken down to free glucose by salivary and intestinal amylases. Glucose is absorbed into the portal blood through an active, energy-requiring mechanism mediated by sodium and a specific glucose transport protein. Fructose is absorbed via the sodium independent GLUT-5 transporter (25). Disaccharide sucrose requires hydrolysis before absorption, which is rapidly accomplished by a plentiful sucrase in the brush border.

Much has been made of the metabolic differences between fructose and glucose in the human body: fructose is rapidly taken up by the liver and bypasses a key regulatory step in glycolysis. There are, however, several points of intersection where the metabolism of fructose and glucose interchange. This metabolic flexibility works to man's evolutionary advantage by allowing a variety of food and energy sources to be processed efficiently. It is only when any single nutrient is consumed to excess and overwhelms the body's metabolic capacity that untoward consequences occur.

Fructose malabsorption appears only to be a problem when too little accompanying glucose is present. This was quickly recognized in early sports drinks formulated solely with fructose to enhance performance by exploiting fructose's low glycemic index. Riby et al (26) subsequently showed that the addition of even small amounts of free or polymeric glucose can ameliorate fructose malabsorption and accompanying gastric distress.

The inability of the body to distinguish fructose-containing nutritive sweeteners from one another once they reach the bloodstream is critical to the HFCS discussion, but often overlooked. Sucrose, HFCS, invert sugar, honey, and many fruits and juices deliver the *same* sugars in the *same* ratios to the *same* tissues within the *same* time frame to the *same* metabolic pathways. Thus, if one accepts the proposition that a given product will be sweetened with one of the fructose-containing nutritive sweeteners, it makes essentially no metabolic difference which one is used.

HIGH-FRUCTOSE CORN SYRUP IS NOT UNIQUELY OBESITY-PROMOTING

If the HFCS-obesity hypothesis is correct, there should be something quantifiably unique about HFCS that is absent from sucrose. The data presented thus far in support of the hypothesis rely heavily on the metabolic comparison of glucose and fructose. It has been known for many years that fructose fed to experimental animals or human subjects in high concentration (up to 35% of calories) and in the absence of any dietary glucose will produce metabolic anomalies (7, 8). The 1994 Fructose Nutrition Review commissioned by the International Life Sciences Institute was highly critical of this line of experimentation (27).

A pure fructose diet is surely a poor model for HFCS, because HFCS has equivalent amounts of glucose. Because no one in the world eats a pure fructose diet, such experimentation must be recognized as highly artificial and highly prejudicial and not at all appropriate to HFCS.

Sucrose is a far more satisfactory model for HFCS. Experiments that test the HFCS-obesity hypothesis in a reasonable way, by comparing it with sucrose, are only now beginning to be published. In a notable current study from 2007, Melanson et al (28) compared the effects of HFCS and sucrose at 30% of calories in 2 randomized 2-d visits in normal-weight women. Concluding that there is nothing uniquely quantifiable about HFCS, they reported no significant difference between the 2 sweeteners in fasting plasma glucose, insulin, leptin, or ghrelin or in energy or micronutrient intake.

HIGH-FRUCTOSE CORN SYRUP IS NOT PREDICTIVE OF US OBESITY

Central to the HFCS-obesity hypothesis is its value in predicting US obesity: Bray et al (10) associated its increased use with increasing obesity rates between 1960 and 2000. But does the association continue beyond 2000?

The Centers for Disease Control and Prevention recently reported that overall, age-adjusted obesity rates obtained from the Behavioral Risk Factor Surveillance System were 15.6%, 19.8%, and 23.7% for 1995, 2000, and 2005, respectively (29). The US obesity crisis continues to worsen. From Figure 2, however, it can be seen that per capita calories from HFCS have been stagnant since 1998 and in decline since 2002. Clearly, the association between HFCS and obesity is no longer valid, and HFCS is not predictive of US obesity.

HIGH-FRUCTOSE CORN SYRUP IS NOT PREDICTIVE OF GLOBAL OBESITY

There is a misconception that HFCS is not only the dominant US sweetener, but the dominant world sweetener as well. Neither is true. HFCS accounts for about one-half of the nutritive sweetener used in the United States, but for only 8% of the nutritive sweetener used worldwide; sucrose accounts for the rest (30). The sugar economy is firmly established in many countries and receives heavy government economic and trade protection from competing sweeteners and technologies. Until recently, Mexico imposed a high use tax on HFCS to protect its domestic sugar industry. In addition, HFCS production requires not only an abundant and consistent starch source, but also the use of sophisticated technology. These conditions are satisfactorily met in only a few geographic locations.

F4 This point is illustrated in **Figure 4**, in which 2005 obesity rates derived from World Health Organization data (31) for 5 non-US countries are plotted against HFCS as a percentage of national nutritive sweetener use (30); US data are provided for comparison. The non-US countries with the highest percentage use of HFCS were South Korea, Japan, and Canada. However, the highest obesity rates were in Mexico and Argentina, the 2 countries with the lowest percentage use of HFCS. Thus, HFCS is not predictive of global obesity either, providing further evidence that the HFCS-obesity hypothesis is not valid. AQ: 4

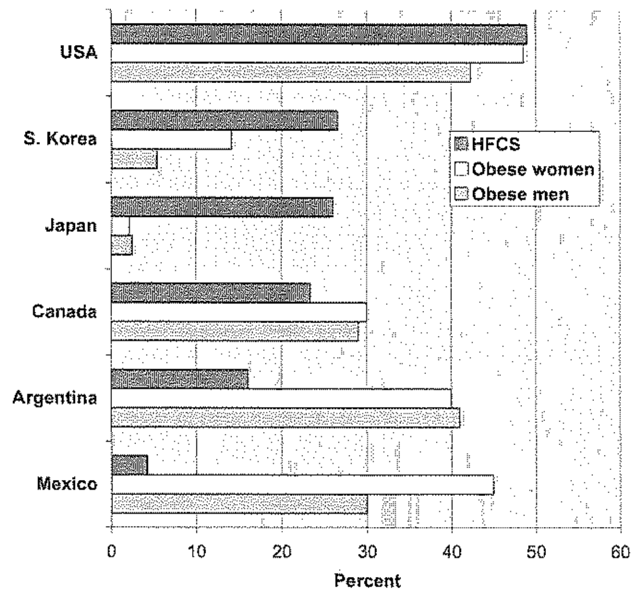

FIGURE 4. World Health Organization obesity rates (BMI ≥ 30 kg/m^2, age ≥30 y) versus high-fructose corn syrup [(HFCS): share of (sucrose + HFCS)] in selected countries for 2005 (30, 31).

ELIMINATING HIGH-FRUCTOSE CORN SYRUP WOULD NOT HAVE A SIGNIFICANT EFFECT ON OBESITY

Nutritive sweeteners are used in foods and beverages for many reasons, including sweetness, mouthfeel, colligative properties (eg, freezing point manipulation), moisture control, crystal structure, bulk, browning, carmelization, color, and fermentable solids. They are not easily replaced in products without risking customer notice and displeasure. One could reasonably assume, then, that if the use of HFCS were to be restricted or entirely eliminated in the United States—as some advocate—an alternative nutritive sweetener with similar physical and functional properties would be sought. Because honey and fruit juice concentrates are produced in such limited quantities, it is likely that companies would revert back to formulas circa 1970 and replace HFCS with sucrose.

What would be the impact on obesity in the United States of a change back to sucrose from HFCS? On the basis of the similarities between sucrose and HFCS noted above, it can be predicted with some certainty that there would be no change in caloric intake, no change in basic metabolism, and no change in rates of obesity. The substitution of sucrose for HFCS would be a nutritional wash. The one change consumers would notice is higher prices as sucrose is substituted for the less-expensive HFCS.

CONCLUSIONS

The hypothesis that HFCS is a unique cause of obesity is not supportable in the United States or elsewhere, and the reasons are clear:

- HFCS has the same sugars composition as other "benign" fructose-glucose sweeteners such as sucrose, honey, and fruit juice concentrates and dietary sources such as fruits and juices;
- Increased caloric intake since 1970 was not due to added sugars (including HFCS) but rather was due to increased consumption of all caloric nutrients, especially fats and flour and cereals;
- HFCS is consumed in equal amounts with sucrose in the United States, but at <10% of the amount of sucrose worldwide;

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- Fructose-glucose sweeteners are metabolized through the same pathways regardless of dietary source;
- Although pure fructose can cause metabolic upsets at high concentrations and in the absence of glucose, such experiments are irrelevant for HFCS, which is not consumed at extreme high levels and contains both fructose and glucose;
- There is no longer an association between HFCS and obesity in the United States: per capita consumption of HFCS has declined in recent years, whereas obesity rates continue to rise; and
- There is absolutely no association between HFCS use and worldwide obesity; HFCS is really a minor sweetener in the global perspective.

No one would disagree that HFCS as a caloric ingredient can lead to weight gain if products sweetened with it are consumed to excess. After all, the same may be said for all caloric ingredients, such as fats, protein, alcohol, and other carbohydrates. But there is absolutely no proof that HFCS acts in any exclusive manner to promote obesity. It is time to retire the hypothesis that HFCS is uniquely responsible for obesity.

Other articles in this supplement to the Journal include references 34–37.

The author is a consultant to the food and beverage industry in nutritive sweeteners, including HFCS and sucrose. His professional associations, past and present, include individual food industry companies as well as such organizations as the American Chemical Society, American Council on Science and Health, Calorie Control Council, Corn Refiners Association, Institute of Food Technologists, and International Life Sciences Institute.

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High Fructose Corn Syrup and Metabolism

Lowndes, J., Zuckley, L.M., Nguyen, V., Angelopoulos, T.J., and Rippe, J.M. June 2007. The Effect of High-Fructose Corn Syrup on Uric Acid Levels in Normal Weight Women. Presented at the annual meeting of the Endocrine Society June 2-5, 2007. Program Abstract #P2-45.

Melanson, K.J., Zuckley, L., Lowndes J., Nguyen, V., Angelopoulos, T.J., and Rippe, J.M. 2007. Effects of high-fructose corn syrup and sucrose consumption on circulating glucose, insulin, leptin, and ghrelin and on appetite in normal-weight women. *Nutrition* 23:103-112.

Zuckley, L.M., Lowndes, J., Melanson, K.J., Nguyen, V., Angelopoulos, T.J., and Rippe, J.M. June 2007. The Effect of High Fructose Corn Syrup on Post-Prandial Lipemia in Normal Weight Females. Presented at the June 2007 Meeting of The Endocrine Society. Program Abstract #P2-46.

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Research Shows HFCS and Sucrose Affect Triglycerides and Uric Acid Similarly*

The Effect of High Fructose Corn Syrup on Post-Prandial Lipemia in Normal Weight Females.

Linda M Zukley[1], Joshua Lowndes[1], Kathleen J Melanson[2], Von Nguyen[1], Theodore J Angelopoulos[1], James M Rippe[1].
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Introduction: Fructose has been implicated in potentially promoting obesity, due in part to its lipogenic effect. Most work has examined the effects of pure fructose rather than high-fructose corn syrup (HFCS), the commonly-consumed form of fructose. A further concern is that postprandial lipemia, a risk factor for cardiovascular disease, may be greater after fructose consumption likely due to hepatic lipogenesis. In the past thirty years HFCS has largely replaced sucrose as the sweetener used in carbonated soft drinks in the USA. The purpose of this study was to compare the effect of HFCS versus sucrose sweetened soft drinks as part of a normal diet on triglycerides in normal weight females.

Methods: Thirty normal weight women (mean age 33.0 10.6 years, mean BMI 22.42 1.65) were studied on two randomized 2-day experimental visits to our metabolic unit during which HFCS and sucrose sweetened beverages were consumed with isocaloric diets on day 1 while blood was sampled. On day 2 of these visits, food was eaten ad libitum. Blood was sampled every 30 minutes for the first 16 hours and then every 60 minutes thereafter. Net area under the curve was calculated using the trapezoidal method after subtracting each value from the baseline value.

Results: No significant differences between the two experimental visits were seen in fasting values of triglycerides (p=NS). The within day variation was not different between the two experimental visits. Net areas under the curve were also similar (p=NS). There were no differences in energy or macronutrient intake on day 2 (ad-libitum feeding).

Discussion: These short-term results suggest that when fructose is consumed in the form of HFCS, there are no differences in the metabolic effects in lean women compared to sucrose. Further research is required to determine if the current findings hold true for obese individuals, or in individuals at risk for the metabolic syndrome.

Program Abstract # P2-46

The Effect of High-Fructose Corn Syrup on Uric Acid Levels in Normal Weight Women.

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Introduction: Over the past 3 decades dietary fructose consumption has increased greatly, a trend coinciding with the emergence of the obesity epidemic. As such, excess fructose consumption has been investigated for its potential causative roll. Recent evidence also suggests a potential link between fructose consumption and the development of the metabolic syndrome, independent of weight gain, as a result of uric acid mediated endothelial dysfunction. Over the past 30 years HFCS has largely replaced sucrose as the sweetener in carbonated soft drinks (CSD) in the USA. The HFCS in CSD represents a major source of fructose in the USA diet. Therefore the purpose of this study was to compare the effects of HFCS when consumed as part of mixed meal, on uric acid levels compared to sucrose consumption.

Methods: Thirty normal weight women (mean age 33.0 10.6 years, mean BMI 22.42 1.65) were studied on two randomized 2-day experimental visits to our metabolic unit during which HFCS and sucrose sweetened beverages were consumed with isocaloric diets on day 1 while blood was sampled. On day 2 of these visits, food was eaten ad libitum. Blood was sampled upon entering the metabolic unit at 9am, and two hours subsequently until 7am the following morning.

Results: No significant differences between the two experimental visits were seen in fasting values of uric acid (p=NS) all of which were within normal limits. The within day variation was not different between the two experimental conditions (HFCS/sucrose). A post-prandial increase in uric acid concentration was only observed after dinner (p=0.013), but this was comparable between the two trials. There were no differences in energy or macronutrient intake on day 2 (ad-libtum feeding).

Discussion: These short-term results suggest that when fructose is consumed in the form of HFCS, there are no differences in the metabolic effects in lean women compared to sucrose. Further research is required to determine if the current findings hold true for obese individuals and males.

Program Abstract # P2-45

**Research presented at the annual meeting of The Endocrine Society June 2-5, 2007.*

Melanson, K.J., Zuckley, L., Lowndes J., Nguyen, V., Angelopoulos, T.J., and Rippe, J.M. 2007. Effects of high-fructose corn syrup and sucrose consumption on circulating glucose, insulin, leptin, and ghrelin and on appetite in normal-weight women. *Nutrition* 23:103-112.

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Applied nutritional investigation

Effects of high-fructose corn syrup and sucrose consumption on circulating glucose, insulin, leptin, and ghrelin and on appetite in normal-weight women

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Abstract

Objective: Fructose has been implicated in obesity, partly due to lack of insulin-mediated leptin stimulation and ghrelin suppression. Most work has examined effects of pure fructose, rather than high-fructose corn syrup (HFCS), the most commonly consumed form of fructose. This study examined effects of beverages sweetened with HFCS or sucrose (Suc), when consumed with mixed meals, on blood glucose, insulin, leptin, ghrelin, and appetite.

Methods: Thirty lean women were studied on two randomized 2-d visits during which HFCS- and Suc-sweetened beverages were consumed as 30% of energy on isocaloric diets during day 1 while blood was sampled. On day 2, food was eaten ad libitum. Subjects rated appetite at designated times throughout visits.

Results: No significant differences between the two sweeteners were seen in fasting plasma glucose, insulin, leptin, and ghrelin ($P > 0.05$). The within-day variation in all four items was not different between the two visits ($P > 0.05$). Net areas under the curve were similar for glucose, insulin, and leptin ($P > 0.05$). There were no differences in energy or macronutrient intake on day 2. The only appetite variable that differed between sweeteners was desire to eat, which had a higher area under the curve the day after Suc compared with HFCS.

Conclusion: These short-term results suggest that, when fructose is consumed in the form of HFCS, the measured metabolic responses do not differ from Suc in lean women. Further research is required to examine appetite responses and to determine if these findings hold true for obese individuals, males, or longer periods.

Keywords: Sweeteners; Sugars; Fructose; Energy balance regulation; Food intake; Hunger; Satiety

Introduction

The consumption of total sugars has increased significantly in the past 30 y in the United States, with shifts in the sources of sweeteners [1,2]. Before the mid-1960s carbonated soft drinks (CSDs) were largely sweetened with sucrose (Suc; 50% glucose and 50% fructose), but currently the leading source of fructose in the diet in the United States is high-fructose corn syrup (HFCS). HFCS-55 used in CSDs contains 55% fructose and 42% glucose [2]. It has been argued that increased consumption of fructose in the diet may be a contributing factor to the dramatic increase in obesity in the United States and other developed countries, because fructose does not stimulate the production and secretion of insulin [3,4].

A role for insulin in the regulation of energy balance and adiposity was postulated in the early 1970s [5], and since this time considerable evidence has supported this hypoth-

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esis. Insulin may influence energy balance through direct actions on the central nervous system that regulate energy intake [6,7] and through its influence on leptin. Insulin-mediated glucose uptake and metabolism in adipose tissue plays a key regulatory role in leptin concentrations [8,9]. Leptin, whose diurnal patterns have been shown to be regulated by insulin [10], is recognized as a medium- to long-term regulator of energy balance through its effects on reducing energy intake and stimulating energy expenditure [11]. Deficits in leptin production have been demonstrated to be associated with increased body adiposity in humans [10,12].

Blood glucose, insulin, and leptin tend to be inversely related to circulating ghrelin in the fasting [13] and fed [14–16] states. Ghrelin, an orexigenic hormone secreted from the enteroendocrine cells of the stomach, is implicated in short-term hunger, food intake, and body weight [17–20]. Ghrelin administration in rodents leads to increased food intake and body weight, and in humans it has been shown to increase food intake [17,21]. Circulating ghrelin is highest in humans in the fasting state, shows premeal increases that are associated with hunger and meal initiation, and is suppressed upon food ingestion [18,21,22]. Carbohydrate-rich meals have been shown to suppress ghrelin and associated subjective hunger more so than fat-rich meals [22,23], which is likely due to effects on glycemia and possibly insulinemia [10,15].

Fructose, unlike glucose, does not stimulate insulin secretion from the pancreatic B cells [24,25]. In a recent study, fructose, consumed with mixed meals, was shown to result in decreased circulating insulin and leptin and to attenuate postprandial suppression of ghrelin in women as compared with dietary glucose [16]. It was concluded that the differential effect of fructose on energy regulatory systems compared with glucose might contribute to increased caloric intake and ultimately contribute to weight gain and obesity during long-term consumption of a diet high in fructose [16]. However, pure fructose and glucose are not commonly consumed, as are Suc and HFCS. Based on these findings [16] and the fact that Suc has been replaced by HFCS to a large extent over the past 40 y, the primary objective of the present study was to compare the effects of HFCS with the effects of Suc on endocrine systems associated with energy balance, including insulin, leptin, and ghrelin, and with appetite through subjective ratings and ad libitum consumption. The aim was to investigate whether HFCS may have more deleterious effects on measured indicators of energy balance control as compared with Suc.

Materials and methods

Study design

This study was a single-site, randomized, prospective, double-blind trial comparing the effects of HFCS-55 (55% fructose) with those of Suc (50% fructose) on circulating concentrations of hormones regulating body weight and appetite (insulin, leptin, and ghrelin) over 24 h. We hypothesized that there would be no significant differences in these energy regulatory systems when comparing HFCS-55 with Suc-sweetened CSDs in healthy-weight female volunteers. The protocol was approved by the Florida Hospital Celebration Health institutional review board, and all subjects signed informed consents.

Subjects

Non-smoking women 20 to 60 y of age with body mass indexes of 19–25 kg/m^2 were recruited. Exclusion criteria included prescription medications, consumption of more than two carbonated soft drinks per day, or enrollment in weight-loss programs during the previous month, or a >5-lb weight loss during the past 3 mo. Other exclusions included a surgical procedure for weight loss at any time or major surgery within 3 mo of enrollment, history of thyroid disease, diabetes, glucose intolerance, cardiovascular diseases, uncontrolled hypertension, gastrointestinal disorders, cancer, eating disorders, pregnancy, lactation, dietary restrictions or allergies that would limit the ability to adhere to dietary requirements of the study, consumption of >14 alcoholic drinks per week, and caffeine dependency. A standard 2-h oral glucose tolerance test was performed to rule out the presence of impaired glucose tolerance in all participants.

Body composition was determined by air displacement plethysmography in a self-contained system comprised of a computer-integrated dual-chambered air plethysmograph equipped with a digital scale (model 2000A, Life Measurements Incorporated, Concord, CA, USA). This equipment and methodology have been validated extensively by reputable research groups over a wide range of test subjects [26,27]. Fasting state multiple measurements were taken, and percent body fat and lean body mass were calculated from body volume as is done with other densitometric methods [28]. To assess baseline dietary intake, all individuals completed a 3-d food record, which was analyzed by registered dietitians trained to use the Nutrient Data System for Research (NDS-R) software (University of Minnesota, Minneapolis, MN, USA).

Each subject underwent two experimental visits in randomized order, spaced 1 mo apart. Both visits included two nights and two days in the clinical metabolic unit (CMU). During the first 24-h period dietary intake was controlled (day 1), and subjective appetite was monitored. For the next 12 h, subjects ate ad libitum (day 2). During day 1, the controlled diet was accompanied by beverages sweetened with HFCS-55 (HFCS condition) or Suc (Suc condition), as described below. Being a double-blind study, neither the subjects nor the investigators knew the identity of the beverages. The blinding was not broken until all analyses were complete.

All studies were conducted during the mid-follicular phase of each subject's menstrual cycle to avoid metabolic and appetitive shifts that may occur during menses, ovulation, and the late luteal phase in many women. Because visits were spaced 1 mo apart, they were scheduled so that each woman was tested on the same day of her cycle for both test days. Subjects maintained normal dietary intake and exercise during the interval between the study sessions.

The 2 d before both test visits were preparation days. The purposes of these days were to ensure that the subjects followed general guidelines well to avoid factors that might affect the measurements during test visits and to ensure that subjects entered each of the two testing visits in as similar a metabolic state as possible. During these 2 d, a standardized diet was followed by all subjects to control for energy and macronutrient intake and to ensure the ability to comply with dietary prescriptions. Volunteers were instructed in detail on diet and physical activity for the preparation days. The diets reflected the energy and macronutrient contents of standardized diets to be fed on the test visits. No alcohol was consumed by subjects on these preparation days, and caffeine was limited to two beverages per day. Physical activity was restricted to $\leq$1 h of moderate to vigorous exercise each day. Upon arrival at the CMU, subjects met with registered dietitians to verify compliance with the preparation diet and activity day instructions.

The test visits commenced on the evening before each experimental session. Subjects entered the CMU at Florida Hospital Celebration Health at 1700 h (day 0). At 1800 h, a standardized dinner was given, with macronutrient distribution reflecting that of the controlled test diets, and energy composition geared to meet one-third of each subject's estimated daily requirement (as described below). They then fasted overnight while staying in the CMU. The next morning (day 1), at 0800 h an intravenous catheter was inserted and kept patent with slow saline infusion to allow for blood sampled over the next 24 h. During this time, the subjects consumed the controlled diet as breakfast, lunch, and dinner, served with the test beverages. These beverages were sweetened with HFCS-55 or Suc as 30% of energy intake. Meals were ingested in entirety within 15 min while subjects were observed for compliance to standardize the timing of data collection. Subjects rated appetite throughout the day by using 10-cm visual analog scales (VASs; described below).

Blood sampling was complete on the morning of day 2, but subjects remained in the CMU until 1900 h. During this time, subjects were given breakfast, lunch, and dinner menus of prepared various foods to be consumed ad libitum during the meal. They were asked to select the foods they wished to eat and to eat as much as they would like. All portions were served in excess. For beverages, they were allowed to choose among decaffeinated coffee or tea, fruit juice, milk (non-fat, 2%, or whole), and water. Menu items were designed to be acceptably palatable, but not especially appealing to the senses, because the intention was for the subjects to select according to physiologic hunger rather than hedonic appeal. However, palatability of these foods was rated by each subject on a VAS. Amounts consumed were determined by weighed differences, but subjects were not aware that their food intake was monitored. Ad libitum intake was only allowed during the three meals of the day to avoid interference with the VAS appetite ratings between meals. Each subject was required to ingest $\geq$1 L of water over the course of each study day. This was necessary to ensure adequate hydration and standardize possible effects of fluid consumption on appetite. The total volume of fluid consumed by each subject was carefully measured.

Diet

Each subject ingested breakfast, lunch, and dinner on day 1, which was the controlled intake day. The nutrient composition of the diet was determined using NDS-R software. At 0900 h they ate a bagel, cream cheese, and scrambled eggs; at 1300 h they ate a chef's salad with turkey, cheese, and a dinner roll; at 1800 h they ate a chicken breast, mashed potato, carrots, and a roll with butter. Total energy intake was individualized according to each subject's estimated daily energy expenditure by using a direct measurement of resting metabolic rate (MedGem, HealtheTech, Golden, CO, USA), along with an activity factor adjustment (1.3). Percentages of energy coming from fat, protein, and carbohydrate were 30%, 15%, and 55%, respectively. The total carbohydrate component consisted of 25% from complex carbohydrate and 30% from HFCS-55 or Suc, which were used to sweeten the beverages served with the meals. Subjects were given periodic 10-cm VASs, timed around meals, between each meal, and at bedtime, to rate hunger, desire to eat, and thirst. These scales were anchored by the statements "not at all" and "extremely."

Blood sampling and analyses

During the first 24 h when the catheter was in place, blood samples were obtained before and after each meal, at 30-min intervals until 1300 h, and then hourly until catheter removal the next morning. This protocol allowed frequent sampling for >6 h after dinner completion, when a nocturnal rise in leptin secretion would be anticipated. For each sample, 1 mL of blood was removed to clear saline from the catheter, and then 5 mL was collected into an Vacutainer tube (Becton Dickinson and Company, Franklin Lakes, NJ, USA) containing ethylene diaminetetra-acetic acid. Plasma glucose was measured with a YSI Glucose Analyzer (Yellow Springs Instruments, Yellow Springs, OH, USA). Plasma samples for analysis of insulin, leptin, and ghrelin were treated with protease inhibitors, centrifuged, aliquoted, and frozen at $-80°C$. Batches were sent on dry ice to Linco Diagnostic Services Inc. (St. Charles, MO, USA) and measured by radioimmunoassay.

Data analysis

A two-way analysis of variance with repeated measures (time and trial) was performed to assess differences in the fluctuations of glucose, insulin, leptin, ghrelin, and VAS appetite ratings with respect to the two trials. Net areas under the curve (AUCs) were calculated using the trapezoidal model for glucose, insulin, and leptin in accordance with the method used by Teff et al. [16]. Absolute AUCs were also calculated for VAS appetite ratings for each trial. Differences in AUC between the two trials were determined using a two-way analysis of variance with repeated measures (trial and order of treatment). Dietary intake was analyzed with paired sample t tests for differences between trials on day 2 (ad libitum feeding). Significance levels were two-sided with an α value equal to 0.05. All data are reported as means ± SD.

Results

Subjects

Characteristics of subjects in the study are listed in Table 1. As dictated by inclusion criteria, oral glucose tolerance test results were normal for all subjects. There were no significant differences in day of the menstrual cycle between the two experimental visits (HFCS visits 10.1 ± 2.3; Suc visits 9.4 ± 2.8). Body weights also did not differ between experimental visits (HFCS visits 135.7 ± 14.5 lb; Suc visits 135.8 ± 14.1 lb).

Blood glucose, insulin, leptin, and ghrelin

No significant differences between the two experimental visits were seen in fasting plasma glucose, insulin, leptin, and ghrelin ($P > 0.05$). As shown in Figures 1 to 4, there were no between-trial differences in within-day variation for the two experimental visits for any of these four variables (interaction $P > 0.05$). Typical nocturnal peaks were seen for leptin and ghrelin, which did not differ between treatments. For all blood variables measured, there were no significant differences between conditions regarding the change from fasted to postprandial values at 30 or 60 min after any of the three meals. After each meal, ghrelin was suppressed in a similar manner by HFCS and Suc. Net AUCs for glucose, insulin, and leptin, which did not differ significantly, are presented in Table 2.

Table 1
Subject characteristics

Variable	Randomized (n = 30)
Age (y)	33.0 ± 10.6
Systolic blood pressure (mmHg)	105.7 ± 19.9
Diastolic blood pressure (mmHg)	71.1 ± 6.4
Waist circumference (cm)	70.5 ± 4.8
BMI (kg/m^2)	22.4 ± 1.7
Weight (kg)	60.2 ± 6.6
Body fat (%)	31.5 ± 6.7
Body fat (kg)	19.1 ± 5.1
Lean mass (kg)	41.3 ± 5.0
Cholesterol (mg/dL)	172.9 ± 37.5
Triacylglycerols (mg/dL)	76.4 ± 34.9
HDL cholesterol (mg/dL)	61.3 ± 12.8
LDL cholesterol (mg/dL)	96.3 ± 29.7
Cortisol (μg/dL)	14.2 ± 6.0
Insulin (μU/mL)	5.0 ± 3.6
Resting metabolic rate (kcal/24 h)	1387.0 ± 220.2

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein

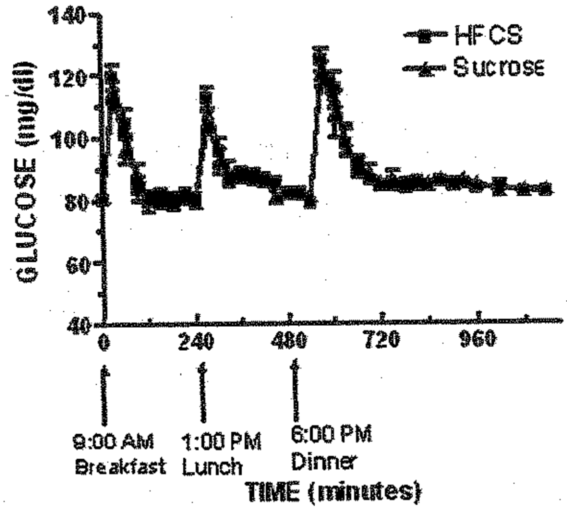

Fig. 1. Plasma glucose concentrations during day 1 of experimental visits in 30 women when consuming HFCS- or sucrose-sweetened beverages as 30% of energy on eucaloric diets. To convert glucose concentrations to millimoles per liter, multiply by 0.556. The calculated area under the curve is presented in Table 2. HFCS, high-fructose corn syrup.

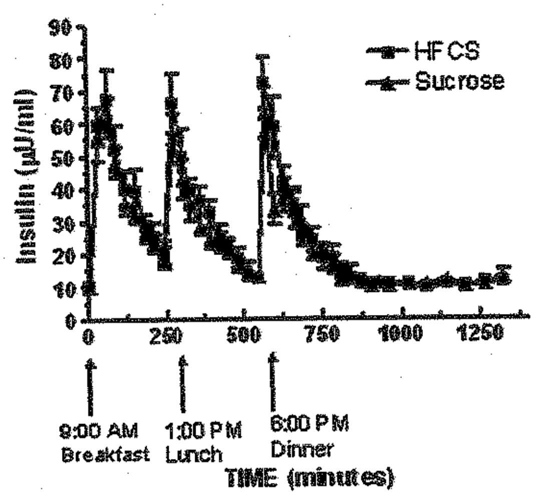

Fig. 2. Plasma insulin concentrations during day 1 of experimental visits in 30 women when consuming HFCS- or sucrose-sweetened beverages as 30% of energy on eucaloric diets. To convert insulin concentrations to micromoles per liter, multiply by 6. The calculated area under the curve is presented in Table 2. HFCS, high-fructose corn syrup.

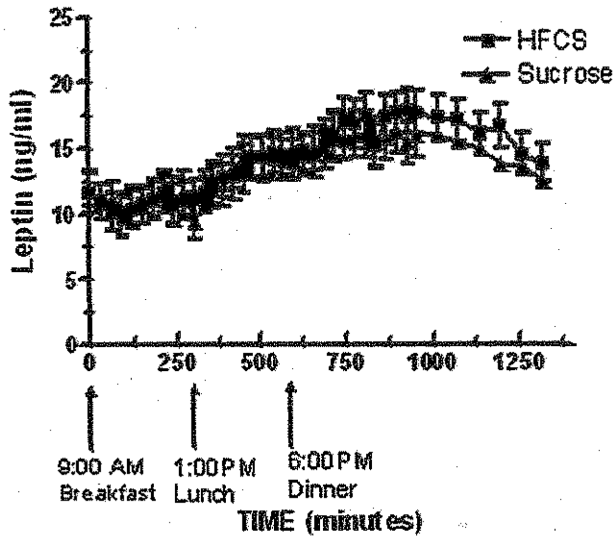

Fig. 3. Plasma leptin concentrations during day 1 of experimental visits in 30 women when consuming HFCS- or sucrose-sweetened beverages as 30% of energy on eucaloric diets. To convert leptin concentrations to nanomoles per liter, multiply by 0.0625. The calculated area under the curve is presented in Table 2. HFCS, high-fructose corn syrup.

Dietary intake

Comparisons of dietary intake between the two experimental visits are presented in Table 3. There were no between-trial differences for any dietary component during ad libitum feeding ($P > 0.05$).

Appetite ratings

As shown in Figures 5 to 7, the within-trial variation in hunger, desire to eat, and thirst ratings were similar between trials for days 1 and 2 (interaction $P > 0.05$). There were no between-trial differences in AUC for VAS appetite ratings except for day 2 desire to eat ($F = 5.776$, $P = 0.023$), which was significantly higher during the Suc condition, as shown in Figure 8.

Effect of treatment order

Of the 30 participants, 16 consumed HFCS on their first experimental visit and 14 consumed Suc on their first visit. In all instances there was no treatment by treatment order interactions (all $P > 0.05$).

Discussion

This study compared the metabolic and appetitive effects of HFCS-55 and Suc under controlled, randomized, double-blinded conditions in non-obese women. In two 2-d experimental visits separated by 1 mo, the women ate isocaloric diets on day 1 with HFCS- or sucrose-sweetened beverages, during which blood was frequently sampled. On day 2 of these visits, women ate ad libitum. VAS appetite ratings were completed throughout the experimental visits. Blood glucose, insulin, leptin, and ghrelin did not differ at any time point between conditions, nor did their AUCs. Similarly, no differences in energy or macronutrient intakes were seen between the visits when the two sweeteners were consumed. The only difference in appetite ratings between the two conditions was a greater desire-to-eat AUC on day 2 after Suc compared with HFCS.

Because prospective epidemiologic data have associated increases in sugar-sweetened beverages with weight gain [29], clinical studies are needed to discern if a causal mechanism exists in this relation. Recently, fructose has been implicated as a sugar that may be responsible, at least in part, for increases in obesity in recent decades, due to its lack of insulin and leptin stimulation, and its failure to suppress ghrelin [3,4]. However, most mechanistic studies have tested pure fructose rather than the more commonly consumed form, HFCS [2]; thus this experiment was designed to examine potential mechanisms in the real-life situations of HFCS and Suc consumption.

Insulin may be a key element in producing a chain of events that leads to increased satiety in the long term [30]. As a result of elevations in blood glucose, increased circulating insulin may amplify satiety through actions within the central nervous system [8,31,32]. Two possible actions have been proposed. The first is through a direct effect on the central nervous system, causing inhibition of food intake, which has been shown in animal models [30,33]. The second is by stimulating leptin. Leptin, secreted by adipocytes, has important regulatory effects in the maintenance of body weight, metabolism, and reproductive function [34] by acting on the central nervous system to inhibit food intake

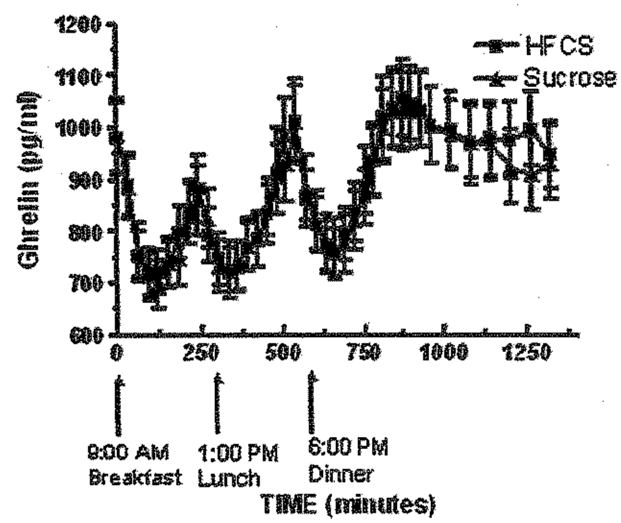

Fig. 4. Plasma ghrelin concentrations during day 1 of experimental visits in 30 women when consuming HFCS- or sucrose-sweetened beverages as 30% of energy on eucaloric diets. To convert ghrelin concentrations to picomoles per liter, multiply by 0.296. HFCS, high-fructose corn syrup.

Table 2
Net AUC* (0900–0700 h) for the 22 h after a fasting baseline sample was collected

	HFCS	Suc	F	P
Glucose (mg/dL) at 22 h	144.83 ± 116.62	121.33 ± 135.67	0.823	NS (0.372)
Insulin (μU/mL) at 22 h	507.98 ± 289.18	436.55 ± 194.19	4.124	NS (0.052)
Leptin (ng/dL) at 22 h	104.35 ± 51.10	92.32 ± 38.73	3.168	NS (0.086)

AUC, area under the curve; HFCS, high-fructose corn syrup; Suc, sucrose
* Net AUC refers to above the baseline value (glucose and insulin) or above the nadir (before 1200 h for leptin).

and activate thermogenesis. Whereas insulin is secreted in acute response to meals, leptin stimulation is delayed for several hours [35,36]. Therefore, leptin may be involved in longer-term energy intake control. Insulin and leptin stimulate central pathways and are secreted in proportion to body adiposity, although circulating levels are also influenced by recent energy intake [30,37,38]. The action of leptin is by the hypothalamus, stimulating energy expenditure from basal metabolism and reducing the drive to eat [11], and potentially inhibiting the effects of the orexigenic hormone ghrelin [39,40]. Inter-relations among insulin, leptin, and ghrelin may provide mechanisms through which short-, medium-, and long-term energy balance controls are linked. Ghrelin, which is secreted primarily by the stomach, has been implicated in the pathogenesis of obesity [22,41,42]. In rodents and in humans, ghrelin has been shown to increase before meal initiation, leading to hunger and food intake, and it subsequently declines after food ingestion [17,21,22,41]. However, in humans, higher body weight is associated with lower ghrelin levels [13], and diet-induced weight loss is associated with elevations in plasma ghrelin, which may promote recidivism [41]. These data indicate a critical role of ghrelin in energy balance, and its relation to dietary factors deserves further research attention.

Consumption of high-fat/low-carbohydrate meals results in lowered 24-h circulating leptin concentrations in normal-weight women compared with low-fat/high-carbohydrate meals [40]. Leptin has also been shown to be reduced after consumption of meals accompanied by beverages sweetened with fructose, a sugar that induces low glycemic responses, as compared with glucose [16]. In the present study, HFCS and Suc consumption resulted in stimulation of insulin and leptin secretion, which was associated with no differences in ad libitum consumption after the day of test sugar consumption. Paradoxically, the AUC for insulin tended to be somewhat higher during the HFCS condition, but this did not reach statistical significance. Two days of appetite ratings were also similar between the test visits, with the exception of desire to eat, which was higher the day after Suc consumption.

A recent weight-loss study in obese individuals showed that a 12-wk high-carbohydrate (65%), low-fat (15%) diet did not result in the expected increases in ghrelin or appetite, suggesting that isocaloric substitution of dietary carbohydrate for fat may lower ghrelin levels and thus hunger [43]. Glucose administration has been shown to lower plasma ghrelin [14,15]. In the present study, HFCS and Suc consumption resulted in similar ghrelin suppression as has been seen in other mixed-carbohydrate feeding studies [23] and in greater ghrelin suppression as compared with a similar study in which pure fructose was fed rather than HFCS [16].

Recent data have suggested that high-fructose intake may be lipogenic [3] and may fail to suppress ghrelin [16]. Pure fructose does not increase plasma glucose or insulin to any great extent. Data from this study showed similar plasma glucose and insulin responses to HFCS-55 and Suc, which contain some fructose and some glucose. The mean glycemic indexes (GIs) of fructose, glucose, and Suc are reported as 19 ± 2, 99 ± 3, and 68 ± 5, respectively (with the reference carbohydrate being glucose) [44]. The GI of HFCS is not published, but the GI of colas sweetened with it is 58 ± 5 [44], which is less than with Suc. Our data

Table 3
Dietary intake during experimental visits for day 1 (calorie and macronutrient controlled feeding) and day 2 (ad libtum feeding)

	Day 1	Day 2		P for between-trial difference for day 2
	HFCS and Suc	HFCS	Suc	
Total energy (kcal)	1790.5 ± 272.2	1884.9 ± 514.0	1802.5 ± 447.1	0.220
Total fat (g)	59.8 ± 9.3	60.7 ± 20.0	55.2 ± 16.9	0.097
Calories from fat (%)	30.1 ± 0.3	29.0 ± 5.3	27.7 ± 5.9	0.255
Total carbohydrates (g)	247.0 ± 37.1	229.8 ± 72.7	224.5 ± 62.7	0.625
Calories from carbohydrates (%)	55.2 ± 0.2	48.5 ± 6.4	49.6 ± 5.7	0.413
Total protein (g)	67.5 ± 10.1	104.6 ± 32.0	101.3 ± 30.9	0.420
Calories from protein (%)	15.1 ± 0.1	22.4 ± 4.7	22.6 ± 4.3	0.830

HFCS, high-fructose corn syrup; Suc, sucrose

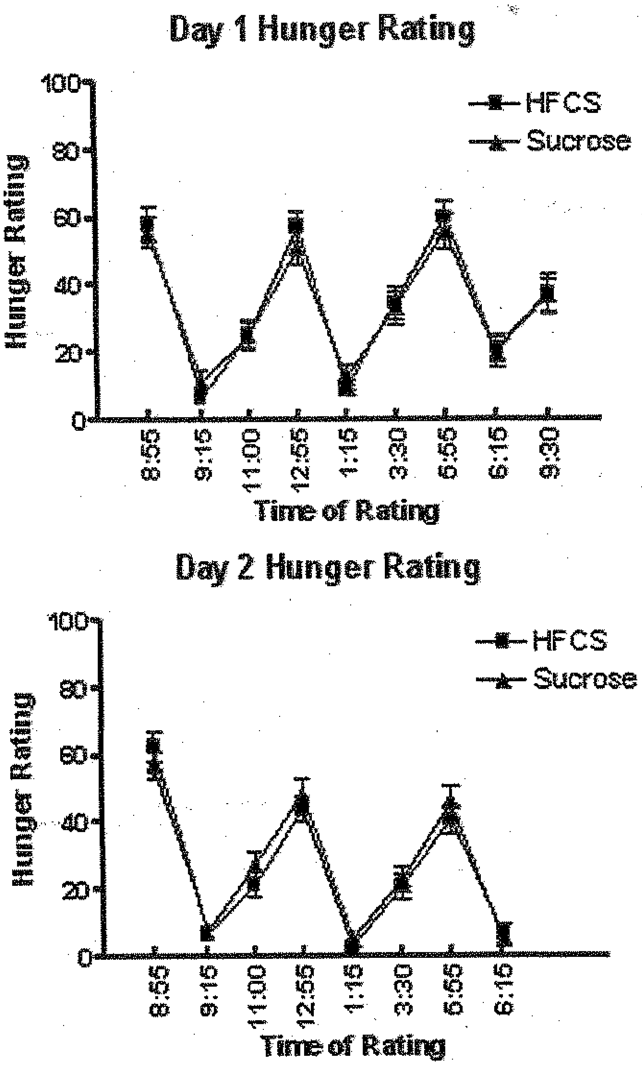

Fig. 5. Time course of hunger ratings from 30 women during 2-d test visits when consuming HFCS- or sucrose-sweetened beverages as 30% of energy on eucaloric diets. (Top) Day 1, when energy intake was controlled; (bottom) day 2 while eating ad libitum (squares, HFCS; triangles, sucrose; interaction $P > 0.05$). HFCS, high-fructose corn syrup.

demonstrate that these two sweeteners do not differ significantly in their glycemic or insulinemic responses when consumed with foods, despite their slight difference in fructose content. Peaks of insulin and glucose secretion after HFCS and Suc in the present study were intermediate as compared with the higher peaks after glucose consumption and lower peaks after fructose consumption seen in the study by Teff et al. [16]. Nadirs of glucose and insulin were similar to those seen in the study by Teff et al. [16]. This is not surprising because the GIs of HFCS and Suc are intermediate as compared with those of fructose and glucose.

In the study by Teff et al. [16], ghrelin was suppressed after the first meal by about 50 and 100 pg/mL for the fructose and glucose meals, respectively. In contrast, in the present study, ghrelin was suppressed by >200 pg/mL after Suc and HFCS meals. This greater ghrelin suppression occurred despite plasma glucose and insulin levels similar to those in the previous study [16]. As mentioned earlier, insulin and glucose have been shown to suppress circulating ghrelin [14,15].

In the present study, appetite ratings did not differ between HFCS and Suc on the days when energy intake was controlled (day 1), as has been reported in comparisons of fructose and glucose [16]. However, on day 2, when subjects ate ad libitum, they expressed a slightly, yet significantly, higher desire to eat the day after Suc as compared with the day after HFCS. The reasons for this difference are not clear. It is unlikely that they are related to the higher GI of Suc, because glycemic responses did not differ significantly between the different sweeteners. The main difference between the sweeteners is in their fructose content (55% in HFCS versus 50% in Suc). Data on the effects of fructose on appetite and energy intake

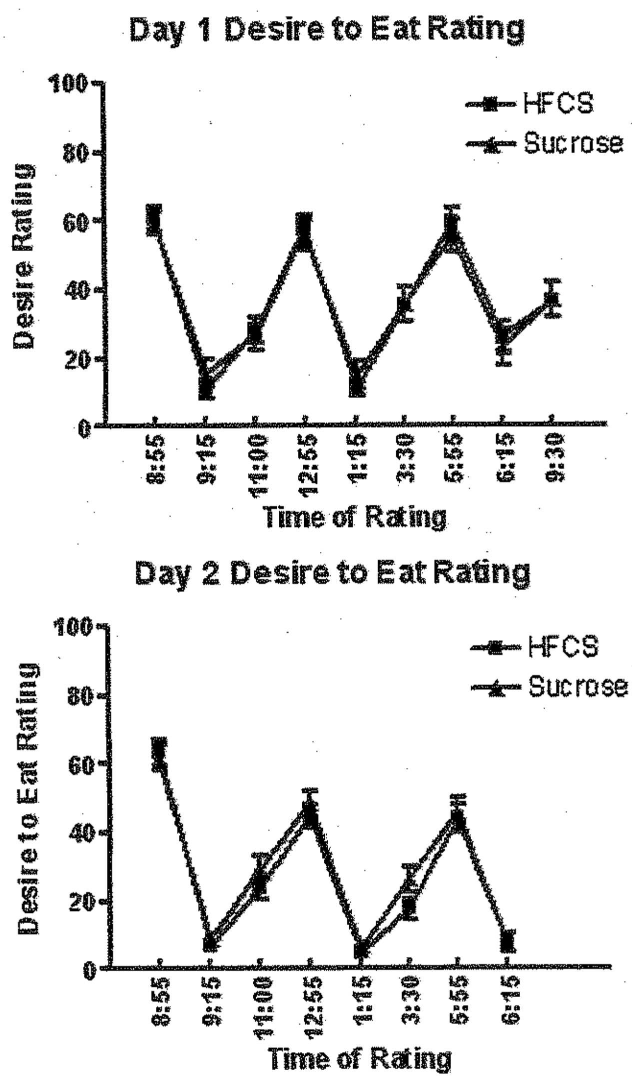

Fig. 6. Time course of desire-to-eat ratings from 30 women during 2-d test visits when consuming HFCS- or sucrose-sweetened beverages as 30% of energy on eucaloric diets. (Top) Day 1, when energy intake was controlled; (bottom) day 2 while eating ad libitum (squares, HFCS; triangles, sucrose; interaction $P > 0.05$). HFCS, high-fructose corn syrup.

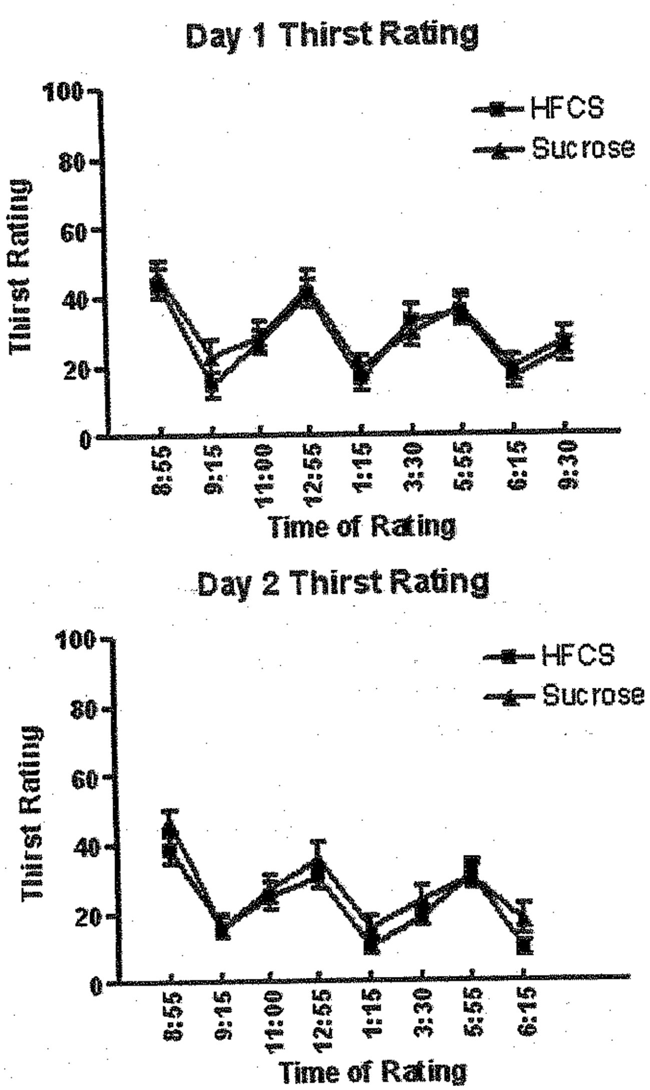

Fig. 7. Time course of thirst ratings from 30 women during 2-d test visits when consuming HFCS- or sucrose-sweetened beverages as 30% of energy on eucaloric diets. (Top) Day 1 when energy intake was controlled; (bottom) day 2 while eating ad libitum (squares, HFCS; triangles, sucrose; interaction $P > 0.05$). HFCS, high-fructose corn syrup.

are conflicting, and data on the effects of HFCS versus Suc are extremely limited. Although some studies have shown decreased appetite with fructose compared with glucose [45–47], others have not [48–50], especially when fructose is consumed in combination with other carbohydrates [16,51,52], as applies to the present study. HFCS and Suc have been associated with increased ad libitum energy intake when compared with non-caloric sweeteners [53,54], but this may be related to their energy content. In the present study, no significant differences in total intakes of energy or macronutrients were seen after a day consuming HFCS versus a day consuming Suc. This corroborates a lack of differences between intakes when the two sugars compared were pure fructose and glucose [16]. Lack of differences between HFCS and Suc treatments in energy intake and hunger ratings are not surprising in the present study due to the similar responses in plasma glucose, insulin, leptin, and ghrelin, all of which have been postulated as metabolic/endocrine signals of energy intake control [55].

Because the present protocol was conducted in healthy-weight women, it cannot be generalized to men or to overweight or obese populations. Thus, additional

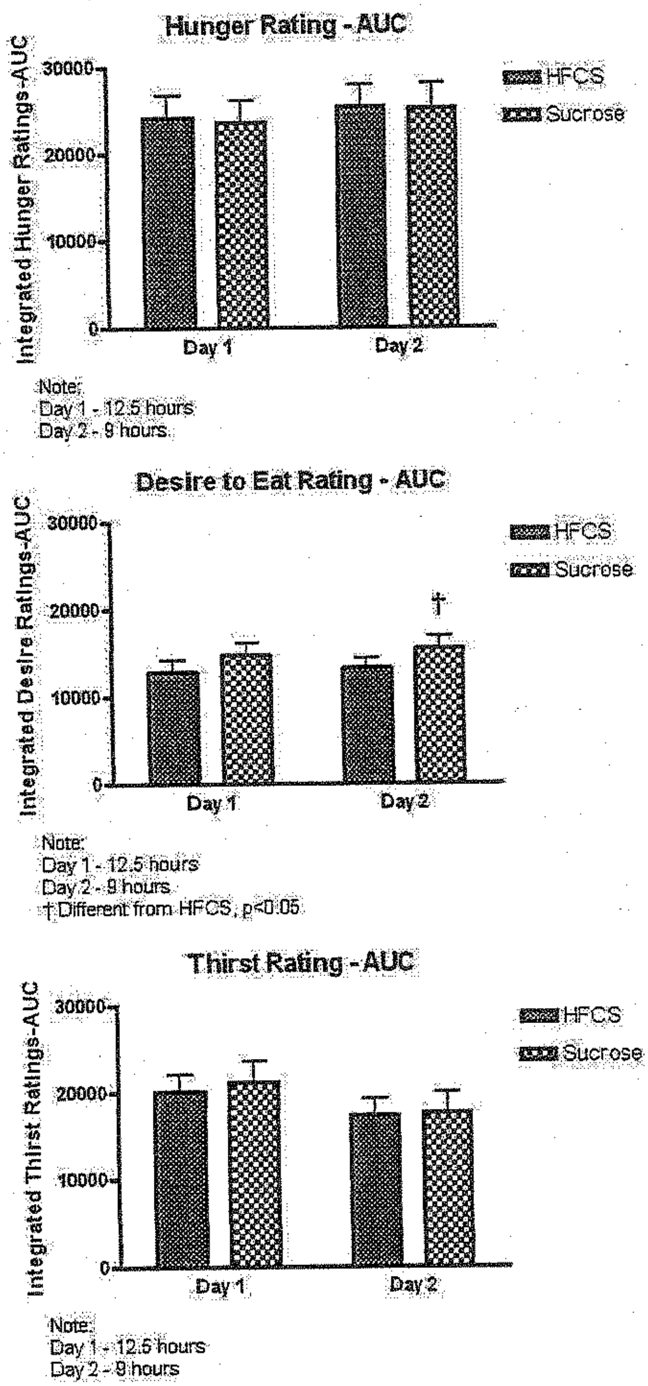

Fig. 8. AUCs for hunger (top), desire to eat (middle), and thirst (bottom) ratings from 30 women during the 2-d test visits (shaded bars, HFCS; cross-hatched bars, sucrose). AUC, area under the curve; HFCS, high-fructose corn syrup.

research should be conducted to examine the effects of HFCS on endocrine regulators of metabolism and appetite in such other groups. Additional metabolic indices should be investigated as mechanistic studies of HFCS continue. Longer-term investigations of the effect of HFCS on energy balance control systems are also needed to further understand the potential effect of this sweetener on body weight.

Summary

In 30 non-obese women, HFCS and Suc resulted in similar circulating glucose, insulin, leptin, and ghrelin levels and appetite over a day when fed as 30% of energy with meals under controlled conditions. On the day after sweetener consumption, ad libitum energy and macronutrient intakes and most appetite ratings were similar.

Acknowledgments

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High Fructose Corn Syrup and Satiety

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Effects of glucose-to-fructose ratios in solutions on subjective satiety, food intake, and satiety hormones in young men[1–3]

Tina Akhavan and G Harvey Anderson

ABSTRACT

Background: The greater prevalence of obesity and the metabolic syndrome in the past 35 y has been attributed to the replacement of sucrose in the food supply with high-fructose corn syrup (HFCS).

Objective: Two experiments were conducted to determine the effect of solutions containing sucrose, HFCS, or various ratios of glucose to fructose (G:F) on food intake (FI), average appetite (AA), blood glucose (BG), plasma insulin, ghrelin, and uric acid (UA) in men.

Design: Sugar solutions (300 kcal/300 mL) were (in %) G20:F80, HFCS 55 (G45:F55), sucrose, and G80:F20 (experiment 1, $n = 12$) and G20:F80, G35:F65, G50:F50, sucrose, and G80:F20 (experiment 2, $n = 19$). The controls were a sweet energy-free control (experiment 1) and water (both experiments). Solutions were provided in a repeated-measures design. AA, BG, and FI were measured in all subjects. Hormonal responses and UA were measured in 7 subjects in experiment 2. Measurements were taken from baseline to 75 min. FI was measured at 80 min.

Results: Sucrose and HFCS (experiment 1) and sucrose and G50:F50 (experiment 2) had similar effects on all dependent measures. All sugar solutions similarly reduced the AA area under the curve (AUC). FI and plasma UA concentrations were significantly ($P < 0.05$) lower after high-glucose solutions than after low-glucose solutions. The lower FI was associated with a greater BG AUC ($P < 0.05$) and smaller AA and ghrelin AUCs ($P < 0.01$). Insulin and BG AUCs were positively associated ($P < 0.001$).

Conclusion: Sucrose, HFCS, and G50:F50 solutions do not differ significantly in their short-term effects on subjective and physiologic measures of satiety, UA, and FI at a subsequent meal. *Am J Clin Nutr* 2007;86:1354–63.

KEY WORDS Fructose, glucose, sucrose, high-fructose corn syrup, blood glucose, insulin, ghrelin, uric acid, appetite, food intake

INTRODUCTION

The increase in the prevalence of obesity in the past 35 y has occurred concurrently with the increased availability of added sugars in the food supply and the increased replacement of sucrose with high-fructose corn syrup (HFCS). Thus, it has been hypothesized that HFCS has contributed to overeating and obesity (1, 2).

However, the role of increased availability of sugars—and specifically of HFCS—in the national food supply, as a significant independent contributor to the current epidemic of obesity, is uncertain for several reasons. First, the availability of sugars has not increased disproportionately to the increased availability of total fat, protein, and energy per capita (3). Second, sugars suppress short-term food intake (FI) in children (4, 5) and adults (6–9), and the magnitude of this effect is inversely related to the glycemic response that those sugars elicit (10, 11). Third, HFCS is a nutritive sweetener containing an unbound form of the same monosaccharides as sucrose (sugar). Sucrose is composed of 50% fructose and 50% glucose linked together by α-1–4 glycosidic bonds. The most common forms of HFCS are HFCS 55% and 42%. HFCS 55%, used primarily in beverages, is composed of 45% glucose and 55% fructose, and HFCS 42%, used primarily in foods, is composed of 58% glucose and 42% fructose (2).

Nevertheless, it is biologically plausible that the ratio of glucose to fructose (G:F) in solutions is a determinant of FI. Fructose does not increase the satiety signals of blood glucose (BG) and insulin to the same extent as does sucrose or glucose do (12–14). Short-term FI is inversely related to the glycemic (10, 11) and insulin (15) responses to sugars, and it has been proposed that fructose does not suppress ghrelin, a gastric appetite hormone (2). Therefore, we hypothesized that high G:F consumed in solutions would lead to a greater response in satiety hormones, subjective satiety, and FI at a later meal than would low G:F, but that there would be no differences among equicaloric solutions containing sucrose, its monosaccaride components, and HFCS.

SUBJECTS AND METHODS

Subjects

Nonsmoking males aged 18–35 y with a body mass index (BMI; in kg/m^2) between 20 and 26 were recruited by postings around the St George campus of the University of Toronto. Subjects who had diabetes (fasting glucose ≥ 7.0 mmol/L) or liver or kidney disease, who had undergone a major medical or surgical event within the past 6 mo, or who were breakfast skippers,

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dieters, or under medication were excluded from all sessions. Restrained eaters were also excluded on their identification by a score of ≥11 on an eating habits questionnaire (16).

Written informed consent was obtained from all subjects. The study protocol was approved by the Human Subjects Review Committee, Ethics Review Office, University of Toronto.

Study design and treatments

Two experiments with a randomized repeated-measures design were conducted. Health young men were randomly assigned to receive 1 of 6 sugar solutions at weekly intervals. In experiment 1, the 4 sugar solutions were HFCS (G45:F55, 75% concentrate; Cargill Sweeteners Company, Wayzata, MN), sucrose (Redpath Sugar; Tate and Lyle North American Sugars, Toronto, Canada), G20:F80, and G80:F20. Two control solutions were used. One was a sweet energy-free control that contained water sweetened with sucralose (McNeil Specialty Products Company, New Brunswick, NJ), and one was water alone (Crystal Springs, Quebec City, Canada). Sweetness was equalized for all treatments except the water control by the addition of 54, 52, 27, and 480 g sucralose to the F20:G80, sucrose, HFCS, and sweetened control solutions, respectively. Sucralose was chosen as a noncaloric sweetener because it has no interaction with carbohydrate metabolism, BG, blood fructose, or insulin secretion and has no effect on the central nervous system (17, 18). To reduce sweetness and improve palatability, lemon juice (Equality; The Great Atlantic and Pacific Company of Canada Ltd, Toronto, Canada) was added. These test solutions were rated equally sweet and equally palatable by a test panel of 8 subjects. In experiment 2, subjects received solutions of G20:F80, G35:F65, G50:F50, sucrose, and G80:F20 as test treatments and water as a control. Treatments were not equalized for sweetness and palatability because no associations and interactions were found in experiment 1 between the sweetness or palatability of treatments and subjective appetite or FI.

Twelve subjects were used in experiment 1, which is consistent with the sample size used in many previous studies in which greater suppression of FI was found after a 75-g preload of sucrose or glucose (6, 10) or a preload of 50 g protein (19) than with the energy-free control. Because the sample size may have been too small to show differences among solutions in experiment 1, we calculated that a sample size of 18 (α error = 0.05; β error = 0.20) was needed for identification of a 120-kcal difference in response between the sugar (G20:F80 and G80:F20) solutions. Therefore, in experiment 2, 19 subjects completed the study sessions.

Sugar solutions contained 300 kcal in 300 mL. In both experiments, treatment formulations used D-glucose monohydrate (Grain Process Enterprises Ltd, Scarborough, Canada) and pure fructose (Now Natural Foods, Bloomingdale, IL). Fructose was not added in proportions of >80% of the sugars in solutions because, when fructose is used alone, even small amounts (eg, 26 g) have resulted in symptoms of nausea and diarrhea in 50% of the population (20, 21). In a pilot study in our laboratory, male subjects reported gastrointestinal discomfort after they consumed 75 g (300 mL) of a G10:F90 solution.

The prepared solutions were stored in the refrigerator overnight and served chilled. An additional 100 mL of water was served after the solutions were consumed to reduce aftertaste.

Protocol

The protocol and procedures are similar to those reported in previous studies (6, 10, 19). Subjects chose a time between 1100 and 1400 at which to participate in the sessions, and they were asked to arrive at the same time and on the same day of the week for all sessions. They were required to fast for 10–12 h and then to consume a standard breakfast 4 h before arrival at the testing facilities of the Department of Nutritional Sciences, University of Toronto. The standard breakfast consisted of a single serving of a ready-to-eat cereal (Honey Nut Cheerios; General Mills, Mississauga, Canada), a 250-mL box of 2%-fat milk (Sealtest Skim Milk; Sealtest, Markham, Canada), a 250-mL box of orange juice (Tropicana Products Inc, Bradenton, FL), and tea or coffee without sugar or sweetener. The subjects were asked not to eat or drink anything between their breakfast and the study session except water, which was allowed up to 1 h before the session. They were also instructed to refrain from alcohol consumption and any unusual exercise and activity the night before a study session.

On arrival, subjects completed questionnaires assessing their sleep habits and stress factors and their compliance with fasting and their pattern of activity on the preceding day. If they reported significant deviations from their usual patterns, they were asked to reschedule. Before subjects consumed the test solutions, they completed visual analogue scale (VAS) questionnaires measuring motivation to eat (7, 22) and physical comfort (7), and a blood sample was obtained. If BG was >6 mmol/L, which suggested that the subject had eaten recently or may be insulin resistant, he or she was rescheduled. Participants were moved to another room (feeding room) where they received one of the test solutions. They were instructed to consume the treatment within 3 min and to return to the experiment room to complete questionnaires assessing the sweetness and palatability of the treatments (6). At 15, 30, 45, 60, and 75 min after consumption of the drinks, the VAS scales were completed and blood samples collected. Subjects remained seated throughout the experimental session and were allowed to read or listen to music.

Pizza (McCain Foods Ltd, Florenceville, NB) and water (Crystal Springs) intakes were measured at an ad libitum lunch 80 min after the subjects consumed the preload solutions. In addition, in experiment 2, to measure thirst before eating, subjects received a bottle of water (500 mL) at 75 min. The bottle was removed and replaced by another before the subjects received the pizza tray.

Three varieties of pizza (Deluxe, Pepperoni, and Three Cheese Deep 'N Delicious pizza; McCain Foods Ltd) were purchased from local retailers. All 3 varieties were similar in contents—averaging 10.0 g protein, 7.6 g fat, 26.6 g carbohydrate, and 226 kcal/100 g energy—and in size (5-in diameter). Because of the lack of a thick outer crust, the pizzas have a uniform energy content that eliminates the possibility that participants would eat the energy-dense filling and leave the outside crust of the pizza. Participants ranked the pizzas according to their preference at screening, and their same choices were provided at each of the 6 sessions. Each pizza (cooked for 8 min at 430 °F and cut in 4 slices) was weighed before serving. Subjects were provided 3 varieties of pizzas to reduce the effect of sensory-specific satiety on test meal intake. The pizzas were served to the subjects on trays at 10-min intervals; in each case, the previous tray was removed and the remaining pizza weighed, until the subjects declined further trays. Each tray contained 2 pizzas of their first choice and 1 pizza each of their second and third choices. Subjects were instructed to eat until they were comfortably full.

The energy intake from the pizza was calculated from the weight consumed and the compositional information provided by the manufacturer. Water intake was measured by weight. Cumulative energy intakes were calculated by adding the energy consumed from the sugar solution to the energy consumed at the test meal. Caloric compensation at the test meal for that consumed in the preloads was calculated by the formula [(kcal consumed at the test meal after the water control – kcal consumed at the test meal after the sugar solution)/300 kcal (in sugar solution)] × 100. A 100% caloric compensation indicates that, at sessions when he was given the 300-kcal treatment, a subject had a lunch intake 300 kcal lower than that at sessions when he was given the control preload. Caloric compensation of <100% indicated that the subject had low compensation for the preload energy at the test meal, whereas scores > 100% indicated overcompensation for preload energy at the test meal.

In each experiment, BG was measured in 12 subjects by finger-prick with the use of a glucometer (Accu-Chek Compact; Roche Diagnostics Canada, Laval, Canada). The same glucometer was used for the same subject for all 6 sessions. Subjects cleaned their fingers before and after each finger-prick with an alcohol swab (Ingram and Bell Medical, Don Mills, Canada). The first drop of blood was wiped off, and the next drop was placed on glucometer strip for measurement of the BG.

To obtain sufficient blood for the measurement of insulin, ghrelin, and uric acid (UA) concentrations in experiment 2, an indwelling intravenous catheter was inserted by a registered nurse into the antecubital fossa vein in the arm of 7 different subjects upon their arrival. The blood samples were drawn into chilled heparinized tubes (Vacutainer; Becton Dickinson, Rutherford, NJ). Two lavender-capped Vacutainer tubes, coated with potassium oxalate–sodium fluoride anticoagulant (EDTA; at 1 mg/mL blood), were used at baseline and 15, 30, 45, 60, and 75 min. For analysis of BG, insulin, and UA, a blood sample was collected in 1 tube (5 mL). For analysis of ghrelin, a separate sample was obtained in a 4-mL Vacutainer tube, and 400 μL aprotinin was added to the tube immediately (<30 s) after blood collection. The tubes were centrifuged at 4 °C for 10–15 min at 2000 × g, and the plasma was stored at −80 °C for analysis. Plasma glucose was measured by using a glucose analyzer (Cobas Integra 800; Roche Diagnostics GmbH, Mannheim, Germany), insulin was measured by using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH), total ghrelin was measured by using a radioimmunoassay (GHRT-89HK; Linco Research Inc, St Charles, MO), and UA was measured by using an enzymatic colorimetric test (11875426 216; Roche Automated Modular Systems, Basel, Switzerland).

Statistical analysis

We used SAS software (version 8.2; SAS Institute Inc, Cary, NC) to conduct the statistical analyses. To test for the effect of the treatments on the outcome variables, one-factor repeated-measures analysis of variance (ANOVA) using the general linear model (PROC GLM procedure) was performed on data for food and water intakes at 80 min, perceived sweetness, palatability of treatments and pizza, physical comfort, and net areas under the curve (AUCs) for average appetite (AA), BG, UA, insulin, and ghrelin. The net AUCs were calculated by applying the trapezoid rule (23), and they included areas over and under the baseline values.

In both experiments, 2-factor repeated-measures ANOVA (GLM) was applied to test for the effects of treatment and time and for treatment × time interaction for AA scores, for the individual VAS used in calculating AA scores, and for BG, insulin, ghrelin, and UA concentrations over 75 min. When an interaction was statistically significant, a one-factor ANOVA using a GLM procedure was followed by Tukey's post hoc test to identify mean differences among treatments at each time of measurement.

In experiment 2, a 2-factor ANOVA (PROC GLM) was performed to determine the effect of the route of blood sampling (finger-prick, $n = 12$; intravenous catheter, $n = 7$) and of treatment on BG, AA, and FI. When venous blood was collected through the indwelling catheter, subjects had significantly lower BG AUC, AA AUC, and FI ($P < 0.01$ for all) than did subjects from whom capillary blood was collected by finger-prick. However, because no significant interaction ($P > 0.05$) was found between treatment and the method of blood sampling, the effect of treatment was consistent across both sampling methods. Therefore, the data for the dependent measures are reported for the pooled sample.

A composite score of the 4 motivation-to-eat VASs was calculated, as described previously by us (6, 10) and others (22), to obtain the AA score. The AA score was reflective of the individual scores on the motivation-to-eat questions and was used here as a summary measure of subjective appetite for analyses.

Correlation analyses of dependent measures were made by using Pearson's correlation coefficients. Significance was set at $P < 0.05$. Data are presented as means ± SEMs.

RESULTS

Subjects

In experiment 1 ($n = 12$) and experiment 2 ($n = 19$), subjects had BMIs of 22.8 ± 0.52 and 24.0 ± 0.37, ages of 29.0 ± 1.33 and 23.6 ± 1.05 y, and weights of 67.6 ± 2.5 and 73.3 ± 1.6 kg, respectively.

Food intake

In both experiments, treatments affected FI. In experiment 1, all sugar solutions except G20:F80 suppressed FI at the test meal significantly ($P = 0.0001$) more than did the water control, but only the G80:F20 and sucrose solutions suppressed FI significantly ($P = 0.0001$) more than did the sweet control (**Table 1**). There were no significant differences in FI among HFCS and the other sugar solutions.

In experiment 2, all sugar solutions except the G20:F80 and G35:F65 solutions suppressed FI at the test meal significantly ($P = 0.0001$) more than did the water control (**Table 2**). Subjects had significantly ($P = 0.0001$) lower FIs after consuming the G80:F20 and sucrose solutions than after consuming the G20:F80 and G35:F65 solutions. However, there were no significant differences in FI between the G50:F50 solution and sucrose or between the G20:F80 and G35:F65 solutions.

Cumulative energy intake

In both experiments, treatments affected cumulative energy intake. In experiment 1, G20:F80 led to the highest cumulative energy intake, although it did not differ significantly from that

TABLE 1
Experiment 1: energy intake, cumulative energy intake, caloric compensation, and water intake after sugar solutions[1]

Solution	Energy intake at test meal[2]	Cumulative energy intake[3]	Caloric compensation[4]	Water intake at test meal
	kcal	*kcal*	*%*	*g*
G20:F80	1207.4 ± 73.4[a,b]	1507.4 ± 73.4[a]	44.5 ± 17.2[b]	416.5 ± 55.6[a,b]
HFCS	1131.9 ± 89.1[b,c]	1431.9 ± 89.0[a,b]	62.7 ± 13.7[a,b]	434.3 ± 54.9[a]
Sucrose	1052.4 ± 75.3[c]	1352.4 ± 75.3[b]	89.2 ± 11.7[a]	348.8 ± 33.4[a,b]
G80:F20	1045.5 ± 83.1[c]	1343.4 ± 83.1[b,c]	92.2 ± 15.5[a]	339.7 ± 27.6[a,b]
Sucralose	1220.0 ± 73.3[a,b]	1220.0 ± 73.3[c]		275.5 ± 40.2[b]
Water	1320.1 ± 83.2[a]	1320.1 ± 83.2[b,c]		327.2 ± 41.3[a,b]
P	0.0001	0.0001	0.05	0.02

[1] All values are $\bar{x}$ ± SEM; $n = 12$. G, glucose; F, fructose; HFCS, high-fructose corn syrup. Solution ratios are by percentage—eg, G20:F80 = 20% glucose:80% fructose. Means in the same column with different superscript letters are significantly different. $P < 0.05$ [one-factor ANOVA (general linear model) for treatment effect, Tukey's post hoc].

[2] Energy (kcal) consumed in a test meal 80 min after treatments.

[3] Energy in solution (kcal) + energy from test meal (kcal).

[4] Calculated by using the formula [(kcal consumed at the test meal after water control − kcal consumed at the test meal after sugar solution)/300 kcal (in sugar solution)] × 100.

with HFCS (Table 1). The HFCS and sucrose solutions did not differ significantly from each other or the water control, but they resulted in significantly ($P = 0.0001$) higher cumulative energy intakes than did the noncaloric sweet control (sucralose). Cumulative intakes did not differ significantly after water or the G80:F20, HFCS, and sucrose solutions.

In experiment 2, the G20:F80 and G35:F65 solutions resulted in significantly ($P = 0.0001$) higher cumulative energy intakes than did the sucrose and G80:F20 solutions, but the energy intakes did not differ significantly from those with the water control or the G50:F50 solution (Table 2). No statistically significant differences in cumulative energy intakes were observed among sucrose, G50:F50, and the water control.

Caloric compensation

In experiment 1, caloric compensation of 92% and 89% for the G80:F20 and sucrose solutions, respectively, was significantly ($P < 0.05$) greater than that of 45% for G20:F80. At 63%, HFCS did not differ significantly from the other sugar solutions (Table 1). In experiment 2, G80:F20 resulted in a caloric compensation (155%) that was significantly ($P = 0.0001$) greater than that of 46%, 41%, and 56% seen for G20:F80, G35:F65 and, G50:F50, respectively (Table 2). Sucrose at 118% did not differ significantly from the other sugar solutions.

Water intake

In experiment 1, subjects had the highest and lowest water intakes at the test meal after HFCS and the sweet control (sucralose), respectively (Table 1). Water intakes after all other solutions were intermediate and not significantly different from either the HFCS or sucralose solution. In experiment 2, neither cumulative water intakes nor water consumed before or within the test meal differed significantly among the treatments (Table 2).

Average appetite score

All sugar solutions except G20:F80 and HFCS (experiment 1) and G50:F50 (experiment 2) lowered subjective AA AUCs significantly ($P < 0.01$) more than did the water control. However,

TABLE 2
Experiment 2: energy intake, cumulative energy intake, caloric compensation, and water intake after sugar solutions[1]

Solution	Energy intake at test meal[2]	Cumulative energy intake[3]	Caloric compensation[4]	Water intake: Before meal	Water intake: Within meal	Water intake: Total
	kcal	*kcal*	*%*		*g*	
G20:F80	1466.8 ± 80.3[a,b]	1766.9 ± 80.3[a]	45.7 ± 22.0[c]	138.5 ± 42.6	379.9 ± 42.1	518.4 ± 54.8
G35:F65	1414.2 ± 85.2[a,b]	1714.2 ± 85.2[a]	41.3 ± 20.9[c]	84.7 ± 27.2	337.2 ± 41.7	421.9 ± 51.1
G50:F50	1375.1 ± 85.9[b,c]	1675.1 ± 85.9[a,b]	55.8 ± 22.7[b,c]	102.4 ± 38.4	374.2 ± 41.8	476.7 ± 52.5
Sucrose	1183.2 ± 60.9[c,d]	1483.2 ± 60.9[b,c]	118.2 ± 11.8[a,b]	20.7 ± 13.6	355.9 ± 50.4	376.6 ± 49.4
G80:F20	1140.5 ± 70.0[d]	1440.5 ± 70.0[c]	154.5 ± 19.4[a]	67.1 ± 33.4	353.2 ± 44.6	420.4 ± 47.1
Water	1603.9 ± 91.9[a]	1603.9 ± 91.9[a,b,c]		40.1 ± 27.3	357.9 ± 36.2	398.0 ± 34.5
P	0.0001	0.0001	0.0001	0.12	0.97	0.15

[1] All values are $\bar{x}$ ± SEM; $n = 19$. G, glucose; F, fructose. Solution ratios are by percentage—eg, G20:F80 = 20% glucose:80% fructose. Means in the same column with different superscript letters are significantly different, $P < 0.05$ [one-factor ANOVA (general linear model) for treatment effect, Tukey's post hoc].

[2] Energy consumed in a test meal 80 min after treatments.

[3] Energy in solution + energy from test meal.

[4] Calculated by using the formula [(kcal consumed at the test meal after water control − kcal consumed at the test meal after sugar solution)/300 kcal (in sugar solution)] × 100.

TABLE 3

Experiments 1 and 2: average appetite area under the curve (AUC) and blood glucose AUC[1]

Solution	Average appetite AUC[2]	Blood glucose AUC[3]
	mm · min	*mmol · min/L*
Experiment 1		
G20:F80	−319.5 ± 322.4[a,b]	109.1 ± 8.6[c]
HFCS	−96.7 ± 319.4[a,b]	154.4 ± 13.0[b]
Sucrose	−397.3 ± 230.3[b]	156.6 ± 12.5[b]
G80:F20	−421.3 ± 254.6[b]	218.8 ± 19.9[a]
Sucralose	332.7 ± 259.3[a,b]	4.8 ± 6.0[d]
Water	463.4 ± 301.4[a]	7.4 ± 4.3[d]
P	0.005	0.0001
Experiment 2		
G20:F80	−521.2 ± 331.2[b]	70.0 ± 10.3[c]
G35:F65	−526.8 ± 303.8[b]	106.8 ± 14.4[b,c]
G50:F50	−112.6 ± 292.4[a,b]	137.1 ± 13.9[b]
Sucrose	−661.3 ± 247.7[b]	142.2 ± 15.5[b]
G80:F20	−802.5 ± 297.5[b]	189.7 ± 17.5[a]
Water	427.0 ± 197.0[a]	2.1 ± 6.9[d]
P	0.0004	0.0001

[1] All values are $\bar{x}$ ± SEM. G, glucose; F, fructose; HFCS, high-fructose corn syrup. Solution ratios are by percentage—eg, G20:F80 = 20% glucose:80% fructose. Means in the same column with different superscript letters are significantly different, $P < 0.05$ [one-factor ANOVA (general linear model) for treatment effect, Tukey's post hoc].

[2] Average appetite net AUC to 75 min after solution consumption (experiment 1, $n = 12$; experiment 2, $n = 19$).

[3] Blood glucose net AUC to 75 min after solution consumption (experiment 1, $n = 12$; experiment 2, $n = 19$).

AA AUCs did not differ significantly among the sugar solutions in either experiment (**Table 3**).

The AA score was significantly ($P < 0.05$) affected by treatment, time, and treatment × time interaction (**Table 4**). The interaction is explained by the significantly ($P < 0.05$) greater and earlier increase in AA score with time after the controls than after the sugar solutions. The decrease from baseline in AA score after the sugar solutions was the greatest at 15 and 30 min; the AA score then returned to baseline or rose above it at 75 min. In both experiments, AA scores at each time did not differ significantly among the sugar solutions over the 75-min span.

Of the individual VASs used in calculating AA scores, only the fullness scale showed a treatment effect in experiment 1, and this was at 75 min (data not shown). The fullness score was significantly ($P < 0.05$) higher after the G20:F80 and sucrose solutions than after the water control, which is consistent with the overall lower AA score (at 75 min) and FI (at 80 min). In experiment 2, fullness, desire to eat, and hunger all showed a significant ($P < 0.05$) effect of treatment. Sucrose, G80:F20, and G35:F65 led to significantly ($P < 0.05$) lower hunger and higher fullness scores than those seen with the water control. Subjects had less desire to eat after sucrose than after water at 75 min (data not shown).

Blood glucose

In both experiments, all sugar solutions resulted in significantly ($P < 0.0001$) higher BG AUC than did the controls (Table 3). In experiment 1, of the sugar solutions, G80:F20 and G20:F80 resulted in the highest and lowest BG AUCs, respectively; sucrose and HFCS were intermediate and did not differ significantly from each other (Table 3). In experiment 2, the highest and lowest BG AUCs were seen after the G80:F20 and G20:F80 solutions, respectively. The BG AUCs for sucrose, G50:F50, and G35:F65 solutions did not differ significantly (Table 3).

In both experiments, BG was significantly ($P < 0.0001$) affected by treatment, time, and treatment × time interaction. In experiment 1, the increase in BG was significantly ($P < 0.0001$) higher after all sugar solutions than after the water and sucralose controls at 15, 30, and 45 min; G80:F20 and G20:F80 resulted in the

TABLE 4

Experiments 1 and 2: baseline and change from baseline average appetite scores after treatments[1]

Solution	Baseline	Change from baseline: 15 min	30 min	45 min	60 min	75 min
				mm		
Experiment 1						
G20:F80	64.5 ± 3.8	−10.9 ± 4.8	−9.1 ± 5.0[b]	−3.4 ± 5.0[a,b]	−0.8 ± 5.5[b]	4.5 ± 5.8
HFCS	57.3 ± 6.7	−8.1 ± 4.6	−6.8 ± 5.2[a,b]	−2.7 ± 5.4[a,b]	5.3 ± 5.6[b]	10.9 ± 6.2
Sucrose	66.1 ± 4.6	−10.7 ± 3.5	−9.0 ± 3.3[b]	−6.3 ± 3.9[b]	−1.9 ± 4.2[b]	2.2 ± 4.5
G80:F20	62.0 ± 4.5	−11.1 ± 3.5	−9.8 ± 4.0[b]	−7.0 ± 4.4[b]	−2.7 ± 4.3[b]	4.9 ± 5.4
Sucralose	59.1 ± 6.8	−3.4 ± 4.8	2.8 ± 3.8[a,b]	5.6 ± 4.2[a,b]	10.1 ± 4.1[a]	13.2 ± 4.4
Water	66.2 ± 4.5	−0.2 ± 2.8	4.8 ± 4.0[a]	10.4 ± 5.3[a]	8.8 ± 5.9[a,b]	13.6 ± 6.1
P	0.38	0.14	<0.01	<0.01	<0.02	0.07
Experiment 2						
G20:F80	68.9 ± 4.4	−16.2 ± 5.1[b]	−12.9 ± 5.4[b]	−5.9 ± 5.5[a,b]	−1.4 ± 5.1[b]	2.4 ± 5.2[b]
G35:F65	71.3 ± 3.0	−11.1 ± 4.9[b]	−9.9 ± 4.9[b]	−8.9 ± 4.9[b]	−5.9 ± 4.8[b]	0.8 ± 4.4[b]
G50:F50	62.5 ± 4.4	−10.5 ± 4.2[a,b]	−8.4 ± 4.2[a,b]	−3.9 ± 4.6[a,b]	−0.1 ± 4.8[a,b]	5.7 ± 4.9[a,b]
Sucrose	69.6 ± 3.3	−12.3 ± 3.2[b]	−12.0 ± 3.8[b]	−11.6 ± 4.2[b]	−8.0 ± 4.6[b]	−1.6 ± 4.2[b]
G80:F20	65.5 ± 3.9	−16.1 ± 4.5[b]	−17.3 ± 4.5[b]	−13.1 ± 4.8[b]	−6.9 ± 5.0[b]	−1.1 ± 4.3[b]
Water	65.8 ± 4.0	0.1 ± 2.2[a]	1.8 ± 2.8[a]	6.6 ± 3.3[a]	12.3 ± 3.8[a]	15.3 ± 3.7[a]
P	0.34	<0.001	<0.001	<0.001	<0.001	<0.001

[1] All values are $\bar{x}$ ± SEM. Experiment 1, $n = 12$; experiment 2, $n = 19$. G, glucose; F, fructose; HFCS, high-fructose corn syrup. Solution ratios are by percentage—eg, G20:F80 = 20% glucose:80% fructose. Treatment, time, and treatment × time interaction were significant, $P < 0.05$ for all [2-factor ANOVA (general linear model)]. Means within a column with different superscript letters are significantly different, $P < 0.05$ [one-way ANOVA (general linear model), Tukey's post hoc].

TABLE 5

Experiments 1 and 2: baseline and change from baseline blood glucose concentration[1]

Solution	Baseline	Change from baseline				
		15 min	30 min	45 min	60 min	75 min
				mmol/L		
Experiment 1						
G20:F80	5.1 ± 0.1	2.8 ± 0.2[b]	2.8 ± 0.3[b]	1.4 ± 0.3[b]	0.2 ± 0.1[b,c]	0.1 ± 0.1[b]
HFCS	5.0 ± 0.2	3.6 ± 0.3[a,b]	3.9 ± 0.3[a]	2.3 ± 0.3[a,b]	0.6 ± 0.3[b,c]	−0.2 ± 0.3[b]
Sucrose	5.2 ± 0.1	3.2 ± 0.2[a,b]	3.7 ± 0.3[a]	2.4 ± 0.4[a,b]	1.2 ± 0.4[b]	0.2 ± 0.3[b]
G80:F20	5.1 ± 0.1	3.7 ± 0.3[a]	4.4 ± 0.3[a]	3.3 ± 0.5[a]	2.5 ± 0.5[a]	1.4 ± 0.4[a]
Sucralose	5.1 ± 0.1	0.2 ± 0.1[c]	0.0 ± 0.1[c]	0.1 ± 0.1[c]	0.1 ± 0.1[c]	0.0 ± 0.1[b]
Water	5.0 ± 0.1	0.2 ± 0.1[c]	0.1 ± 0.1[c]	0.1 ± 0.1[c]	0.1 ± 0.1[b,c]	0.0 ± 0.1[b]
P	0.7	<0.0001	<0.001	<0.0001	<0.0001	<0.001
Experiment 2						
G20:F80	4.8 ± 0.2	1.6 ± 0.2[b]	1.7 ± 0.3[c]	1.0 ± 0.2[c,d]	0.4 ± 0.2[c,d]	0.0 ± 0.2[b]
G35:F65	4.8 ± 0.2	2.3 ± 0.3[a,b]	2.7 ± 0.3[b,c]	1.6 ± 0.4[b,c]	0.5 ± 0.3[b,c,d]	0.1 ± 0.1[b]
G50:F50	4.7 ± 0.2	2.5 ± 0.3[a,b]	3.5 ± 0.3[a,b]	2.2 ± 0.3[b]	0.9 ± 0.2[b,c]	0.1 ± 0.2[b]
Sucrose	4.9 ± 0.1	2.5 ± 0.3[a,b]	3.1 ± 0.4[a,b]	2.2 ± 0.4[b]	1.4 ± 0.3[a,b]	0.7 ± 0.2[a,b]
G80:F20	4.8 ± 0.2	2.6 ± 0.4[a]	3.9 ± 0.3[a]	3.4 ± 0.4[a]	2.1 ± 0.3[a]	1.3 ± 0.3[a]
Water	4.8 ± 0.2	0.0 ± 0.1[c]	0.0 ± 0.1[d]	0.1 ± 0.1[d]	0.0 ± 0.1[d]	0.1 ± 0.1[b]
P	0.6	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

[1] All values are $\bar{x}$ ± SEM. Experiment 1, n = 12; experiment 2, n = 19. G, glucose; F, fructose. Solution ratios are given by percentage—eg, G20:F80 = 20% glucose:80% fructose. Treatment, time, and treatment × time interaction were significant, $P < 0.0001$ for all [2-factor ANOVA (general linear model)]. Means within a column with different superscript letters are significantly different, $P < 0.05$ ([one-factor ANOVA (general linear model), Tukey's post hoc].

highest and lowest BG responses, respectively (**Table 5**). At 60 and 75 min, BG remained significantly ($P < 0.0001$) higher than the water control only after the G80:F20 solution. Sucrose and HFCS resulted in an intermediate and identical significant ($P < 0.0001$) increase in BG. In experiment 2, BG was significantly ($P < 0.0001$) higher after all of the sugar solutions—except the G20:F80 (at 45 and 60 min) and G35:F65 (60 min) solutions—than after the water control at 60 min (Table 5). However, at 75 min, BG was significantly ($P < 0.0001$) higher than the water control only after the G80:F20 solution. There was no significant difference between G50:F50 or sucrose at any time.

Uric acid

Except for the G80:F20 solution, all sugar solutions increased the UA AUC significantly ($P < 0.0001$) more than did the water control (**Table 6**). Of the sugar solutions, G80:F20 and G20:F80 had the lowest and highest UA AUCs, respectively. UA AUCs did not differ significantly after the G35:F65, G50:G50, and sucrose solutions.

UA concentrations were significantly ($P < 0.05$) affected by treatment, time, and treatment × time interaction. The solutions containing G20:F80 (at all times) and G35:F65 (at 30, 45, and 75 min) resulted in significantly ($P < 0.05$) greater increases in UA concentrations than did the solutions containing G80:F20 (**Figure 1**). At 75 min, UA concentrations were highest after G20:F80. The sucrose and F50:G50 solutions each resulted in significantly ($P < 0.05$) lower UA concentrations than did the G20:F80 solution, but they did not differ significantly from any other solutions.

Insulin

Of the sugar solutions, G80:F20 solution had the highest and G20:F80 and G35:F65 solutions had the lowest insulin AUCs (Table 6). The G50:F50 and sucrose solutions did not differ significantly from each other or from any other sugar solution.

Insulin concentrations were significantly ($P < 0.05$) affected by treatment, time, and treatment × time interaction. All sugar

TABLE 6

Experiment 2: effect of sugar solutions on the area under the curve (AUC) for uric acid, insulin, and ghrelin[1]

Solution	Uric acid AUC	Insulin AUC	Ghrelin AUC
	μmol · min/L	*pmol · min/L*	*pg · min/mL*
G20:F80	3350 ± 389[a,2]	10460 ± 1250[b]	−11383 ± 3457[b]
G35:F65	2354 ± 581[a,b]	12638 ± 2218[b]	−12063 ± 2695[b]
G50:F50	1550 ± 525[b,c]	15208 ± 2494[a,b]	−14808 ± 3727[b]
Sucrose	1668 ± 300[a,b,c]	16593 ± 1796[a,b]	−10093 ± 2828[b]
G80:F20	334 ± 186[c,d]	20583 ± 3093[a]	−8753 ± 2034[b]
Water	−474 ± 352[d]	−218 ± 369[c]	1848 ± 1199[a]
P	0.0001	0.0001	<0.001

[1] Experiment 2, n = 7. G, glucose; F, fructose. Solution ratios are given by percentage—eg, G20:F80 = 20% glucose:80% fructose. Means in the same column with different superscript letters are significantly different, $P < 0.05$ [one-factor ANOVA (general linear model), Tukey's post hoc].

[2] $\bar{x}$ ± SEM (all such values).

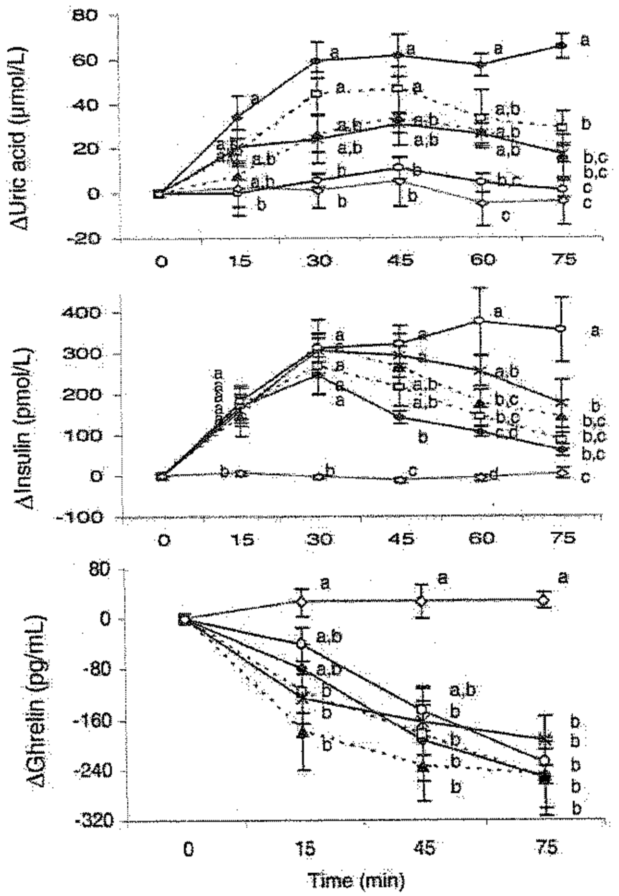

FIGURE 1. Effect of sugar solutions on plasma uric acid, insulin, and ghrelin in experiment 2. Solutions were glucose (G) and fructose (F) at ratios of G20:F80 (◆), G35:F65 (□), G50:F50 (▲), sucrose (*), G80:F20 (○), and water (◇). Δ, change. Mean plasma uric acid, insulin, and total ghrelin at baseline were 295.9 ± 8.5 μmol/L, 45.3 ± 3.8 pmol/L, and 733.4 ± 40.7 pg/mL, respectively. Significant treatment, time, and treatment × time interaction effects ($P < 0.05$ for all) were found by 2-factor ANOVA (general linear model, GLM). One-factor ANOVA (GLM) followed by Tukey's post hoc was used to differentiate the effect of treatment at each measured time. Means at the same time with different superscript letters were significantly different, $P < 0.05$ ($n = 7$).

solutions increased insulin concentrations at 15, 30, and 45 min significantly ($P < 0.05$) more than did the water control. The G20:F80 solution resulted in significantly ($P < 0.05$) lower insulin concentrations than did the sucrose and G80:F20 solutions at 45 min (Figure 1). At 60 min, insulin concentrations after the G20:F80 solution did not different from those after the control. At 75 min, insulin concentrations remained significantly ($P <$ 0.05) higher than those after the control only after the G80:F20 and sucrose solutions, but there were no significant differences among G20:F80, G35:F65, sucrose, and G50:F50.

Ghrelin

All sugar solutions resulted in significantly ($P < 0.05$) lower ghrelin concentrations than did the water control. Thus, the ghrelin AUC was negative and significantly ($P < 0.05$) larger after all sugar solutions than after the water control (Table 6).

Ghrelin concentrations were significantly ($P < 0.05$) affected by treatment, time, and treatment × time interaction (Figure 1). The interaction appears to be explained by a significantly ($P <$ 0.05) greater and earlier suppression in ghrelin by sucrose and G50:F50 than by G80:F20 and G20:F80, but no sugar solutions resulted in a significant difference in ghrelin concentrations at 30 min. All sugar solutions except G80:F20 (at 15 and 45 min) and G20:F80 (at 15 min) resulted in significantly ($P < 0.05$) lower ghrelin concentrations than did the water control.

Relations among dependent measures

FIs were positively correlated with AA score at 75 min (experiment 1: $r = 0.42$, $P < 0.001$; experiment 2: $r = 0.27$, $P <$ 0.005), and inversely correlated with BG (experiment 2: $r =$ -0.41, $P < 0.01$) and insulin (experiment 2: $r = -0.39$, $P <$ 0.05) concentrations at 45 min. FIs were inversely correlated with BG AUC (experiment 1: $r = -0.30$, $P < 0.01$; experiment 2: $r = -0.38$, $P < 0.0001$) (**Figure 2**). The lower AA as reported by AUC was correlated with lower FIs (experiment 1: $r = 0.41$, $P < 0.001$; experiment 2: $r = 0.18$, $P = 0.06$) and higher BG AUCs (experiment 1: $r = -0.29$, $P < 0.05$; experiment 2: $r =$ -0.31, $P < 0.001$) (Figure 2).

In the subsample ($n = 7$) in experiment 2, insulin AUC was positively correlated with BG AUC ($r = 0.51$, $P < 0.001$). At 15 min, insulin concentrations were correlated with BG ($r = 0.60$, $P < 0.001$) and UA ($r = 0.32$, $P < 0.05$) concentrations. At 45 min, insulin concentrations were positively correlated with BG concentrations ($r = 0.48$, $P < 0.01$) and inversely correlated with FIs at the test meal ($r = -0.39$, $P < 0.05$). At 75 min, insulin concentrations were significantly correlated with BG ($r = 0.73$, $P < 0.0001$). The magnitude of the decrease in ghrelin as measured by AUC was positively correlated with the reductions in AA AUCs ($r = 0.60$, $P = 0.0001$) and FIs ($r = 0.40$, $P < 0.01$). At 45 min, plasma ghrelin concentrations were inversely correlated with BG concentrations ($r = -0.30$, $P = 0.05$) and positively correlated with FIs at the test meal ($r = 0.42$, $P < 0.01$).

DISCUSSION

These studies do not support the hypothesis that the replacement of sucrose with HFCS as a caloric sweetener has contributed to overeating and obesity because of differences in their short-term physiologic affects (2). The equicaloric solutions of HFCS, F50:G50, and sucrose were similar in their effects on subjective measures of satiety, blood concentrations of physiologic signals of satiety and of UA, and short-term FIs. However, high G:F in isocaloric sugar solutions resulted in higher BG and insulin concentrations and lower UA concentrations and FIs than did low G:F.

Sucrose, HFCS, and G50:F50 solutions induced similar BG and hormonal responses and decreases in subjective satiety and FIs at the test meal. Sucrose and HFCS were similar to each other in their effects on BG in experiment 1, and it would be expected that the insulin responses were similar because it was previously shown that sucrose and HFCS have similar effects on postprandial BG and insulin concentrations (24). Furthermore, when sucrose or HFCS beverages were served at meals to make up ≈17% of the energy, no differences were found in BG, insulin, leptin, and ghrelin concentrations measured at frequent intervals over 24 h (25). In experiment 2, a solution of G50:F50 was compared with sucrose because, when sucrose is added to acidic solutions, as in soft drinks or fruit-flavored drinks, that sucrose is primarily hydrolyzed before consumption (26). Again, the disaccharide

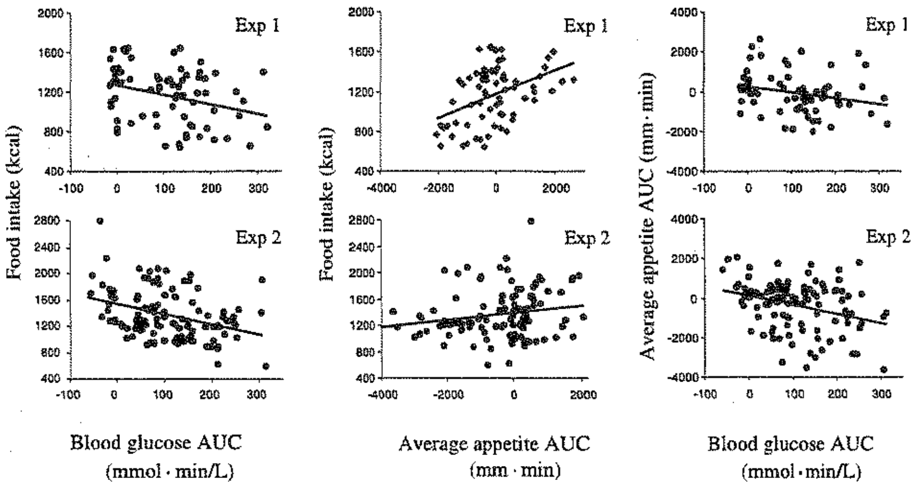

FIGURE 2. Associations between the blood glucose (BG) area under the curve (AUC; mmol · min/L) and food intake (FI; kcal): Experiment 1 (Exp 1): $n = 12$ ($r = -0.30$, $P < 0.01$); experiment 2 (Exp 2): $n = 19$ ($r = -0.38$, $P < 0.001$). Associations between average appetite (AA) AUC (mm · min) and FI (kcal): Exp 1: $n = 12$ ($r = 0.41$, $P < 0.001$); Exp 2: $n = 19$ ($r = 0.18$, $P = 0.06$)]. Associations between BG AUC (mmol · min/L) and AA AUC (mm · min): Exp 1: $n = 12$ ($r = -0.29$, $P < 0.05$); Exp 2: $n = 19$ ($r = -0.31$, $P < 0.001$). Associations were calculated by using Pearson's correlation coefficients.

and the monosaccharide mixtures led to the same results in all dependent measures.

Both experiments showed greater suppression of FI and increased caloric compensation associated with higher G:F ratios in solutions. All sugar solutions except the low-glucose-containing sugar solutions (G20:F80 and G35:F65) led to lower FIs at 80 min than did the water control. These results are consistent with previous reports that 75-g sucrose and glucose solutions, but not a G20:F80 solution, suppressed FIs 60 min later (6, 10) and that FI shortly after the consumption of sugar solutions is inversely related to the effect of sugar solutions on BG (11). The results contrast with reports that solutions containing fructose alone suppress FI at a later meal more than do glucose solutions (12). However, in these comparisons, this effect of fructose was due to its slow absorption when consumed in the absence of glucose, which resulted in gastrointestinal distress (19). For this reason, a solution of fructose alone was not included in the present studies

All sugar solutions increased BG and insulin and reduced ghrelin more than did the control. Although BG may contribute directly to satiety (7, 8), it is clearly not the only reason for the more favorable effects of the high-glucose solutions than of the high-fructose solutions on FI. High-glucose treatments and the higher BG responses derived from them also were associated with greater responses in the satiety hormone insulin and a decrease in the orexigenic hormone ghrelin. However, the role of BG and insulin in the suppression of ghrelin remains uncertain for several reasons. Although a previous study reports that glucose at 15% of the energy in meals (27) leads to lower postprandial ghrelin than does fructose at 15% of the energy in meals, this association does not define the mechanism controlling the suppression of ghrelin secretion. In the present study, insulin and ghrelin responses were not found to be inversely related, and this observation is consistent with more recent data showing that, whereas the presence of insulin is required, a postprandial insulin response is not required, and nutrient sensing by ghrelin-producing cells is an important regulator of ghrelin secretion (28). For example, fat ingestion leads to ghrelin suppression but does not increase postprandial insulin (29). Our data support the proposed role of ghrelin-producing cells in nutrient sensing, because all sugar solutions suppressed ghrelin similarly, even though BG and insulin were higher in the high-glucose than in the low-glucose solutions.

Plasma UA was measured because replacement of sucrose with HFCS has been suggested to play a causal role in the metabolic syndrome (30). Fructose consumption increases plasma UA by increasing purine biosynthesis and decreases renal clearance of UA by increasing plasma lactate concentrations (31). In the present study, all sugar solutions except the G80:F20 solution significantly increased UA above control values and the fructose content of the solutions associated positively with UA AUC ($r = 0.69$, $P < 0.0001$) and inversely with insulin AUC ($r = -0.54$, $P < 0.001$). However, the G50:F50 and sucrose solutions increased UA AUC equally, which suggests that a significant difference between HFCS and sucrose is unlikely. Therefore, whereas greater intakes of fructose may elevate plasma UA, as reported previously (31), the substitution of HFCS for sucrose is an unlikely contributor to the metabolic syndrome by this mechanism.

The differing G:F in solutions did not affect water consumption. The observation that subjects in experiment 1 drank more water at their meal after the HFCS than after the sweet control was pursued in experiment 2 because it was possible that fructose, because of its slower absorption compared with that of glucose (32), created a hyperosmolar environment in the small intestine and thus caused the retention of fluid, feelings of thirst, and gastrointestinal discomfort (19). Because all sugar solutions resulted in similar water intake before and during the test meal in experiment 2, the differences found between HFCS and the sucralose solution in experiment 1 were attributed to reduced thirst after the sucralose solution and not to increased thirst due to fructose in the sugar solutions. Although there is no mechanism to account for this effect of sucralose, it does not appear to be unique because, when consumed during a meal, aspartame-sweetened drinks reduced thirst more than did sucrose-sweetened drinks (33).

Sweetness was not equalized among solutions in experiment 2 because it was proposed that the greater sweetness of fructose would also be an independent factor affecting FI (2). However, no significant relation was found between the sweetness ($r = -0.06$) and palatability ($r = 0.13$) of treatments and FI at the test meal, as expected if the time interval between treatment and FI is >1 h (34). In experiment 1, whereas the sweetness of all solutions except the water control was equalized with the sweetest solution (G20:F80), sweetness was reduced by adding lemon juice. The subjects judged the palatability of the test solutions to be equal to the water control.

High FIs by young men given test meals after an overnight fast and a light breakfast have been reported in many studies, but this has not been found to compromise treatment effects (6–8, 10–11). The higher FIs in experiment 1 than in experiment 2 may be due to several reasons. First, experiment 1 was conducted in the summer, and experiment 2 was conducted in the winter. Higher ambient temperatures are associated with lower FIs than are low ambient temperatures (35). Second, on average, subjects came in 2 h later in experiment 2. Therefore, the test meal later in the day would also contribute to greater hunger and FI. Third, subjects in experiment 2 were on average 5.4 y younger ($P < 0.004$) and 5.7 kg heavier ($P < 0.06$) and had a BMI 1.2 greater ($P < 0.06$) than did subjects in experiment 1. Appetite and FI are reduced by age (36) and are increased in association with body weight and the duration of fasting (37). The overall treatment effects in the 2 experiments were similar, however, which suggests that these differences in characteristics and FIs between the 2 samples did not affect the outcomes.

In conclusion, solutions of HFCS, F50:G50, and sucrose were similar in their effects on subjective measures and physiologic signals of satiety, plasma UA concentrations, and FIs in young men. However high G:F in isocaloric sugar solutions result in higher BG and insulin concentrations and lower UA concentrations and FIs than did low G:F.

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The authors' responsibilities were as follows—GHA: conceiving the hypothesis, designing the experiment, and writing the manuscript; and TA: conducting the experiments, collecting and analyzing the data, and writing the manuscript. GHA serves as the chair of the board of the International Life Sciences Institute and as a science advisor to the Canadian Sugar Institute and to Archer Daniels Midland (a producer of HFCS); he has no equity or other financial interests in either industry. GHA also has received unrestricted research grant funding from the US Sugar Association and the Canadian Sugar Institute. TA had no personal or financial conflict of interest.

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Hunger, thirst, and energy intakes following consumption of caloric beverages

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Abstract

Whereas soft drinks are described as primarily thirst-quenching liquids, juices and milk are said to be liquid foods, with a greater satiating power. This study was conducted to compare the effects of orange juice, low-fat milk (1%), regular cola, and sparkling water on hunger, thirst, satiety, and energy intakes at the next meal. Thirty-two volunteers (14 men and 18 women), ages 18–35 years, consumed a breakfast preload composed of 590 ml (20 oz) of an energy-containing beverage (1036 kJ) or water (0 kJ) and a slice of toast (418 kJ) on four different occasions. Participants rated hunger, thirst, fullness, and desire to eat at baseline and at 20-min intervals for 2 h following preload ingestion. A tray lunch was presented at 2 h, 15 min and food consumption was measured. Compared to sparkling water, the three energy-containing beverages were associated with higher fullness and reduced hunger rating and desire to eat. However, energy intakes at lunch (4511 ± 151 kJ for men and 3183 ± 203 kJ for women) were the same across all four beverage conditions and no compensation for breakfast energy was observed. The three beverages of equal energy value were significantly different from sparkling water, but not from each other, in their effects on hunger and satiety ratings. All four beverages satisfied thirst equally well. Whether energy-containing cola, juice, and low-fat milk facilitate a positive energy balance remains a topic for further study.

Keywords: Energy-containing beverages; Soft drinks; Energy compensation; Hunger; Thirst; Satiety

1. Introduction

Energy density of foods, measured in terms of kilojoules per unit weight, is said to influence daily energy intakes more than any other factor [1–4]. Energy density depends almost entirely on the foods' water content [5]. Lower energy-density foods are said to have greater satiating power so that participants are able to "feel full on fewer calories" [1].

Foods with a high water content have an impact on both satiation and satiety [1]. Reducing energy density of an entrée through addition of vegetables to a pasta salad led to increased satiation, as measured by lower energy intakes during that meal [2–4]. Reducing energy density of a preload, such as a milk beverage, led to increased satiety, defined as lower food consumption at the next eating occasion [6]. Rolls and Barnett [1] found that soups, milk-based drinks, and vegetable and fruit juices helped people feel full and eat less at the next meal. Lowering energy density of the diet may be a promising strategy for weight control [1,5].

Energy-containing beverages, juices, and milk are mostly water and deliver relatively little dietary energy per gram [5]. One might expect beverages to be useful in lowering energy density of the total diet [5]. However, there is no agreement as to the impact of liquid calories on satiety [7–9]. Whereas some researchers believe that liquid foods are good choices for promoting satiety [10,11], others believe that physiological compensation for liquid energy is imprecise and incomplete [9,12,13]. The latter view holds that low energy-density beverages have less impact on satiety than do energy-dense solid foods.

To deal with this seeming paradox, researchers have proposed that some beverages had a lesser impact on satiety than others. Soft drinks were described as primarily thirst-quenching liquids [1] that failed to trigger satiety mechanisms regulating food consumption. Rising rates of childhood and adolescent obesity were blamed on the failure of

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physiological satiety and the lack of accurate compensation for sugar energy consumed in the form of caloric soft drinks [14]. In contrast, sugar energy consumed in the form of fruit and vegetable juices was said to satisfy hunger [1,11]. Rolls et al. [1,10,11,15] noted that soup and vegetable juices effectively suppressed food consumption at lunch and that milk-based beverages also tended to be satiating. Milk and juices were characterized as "foods that you drink" [1].

There are no published data to support, or disprove, this point of view. Energy densities of low-fat (1%) milk (1.8 kJ/g), orange juice (1.8 kJ/g), and regular cola (1.8 kJ/g) are almost exactly the same [1,5]. If milk, fruit juice, and soft drinks have a differential impact on hunger and satiety, then, factors other than energy density must be involved.

Most studies on the short-term regulation of food intake made use of the preload paradigm [16–18]. Energy density was manipulated by varying preload volume at constant energy or varying preload energy at constant volume [3,19–21]. Preload energy was often manipulated using sugar or fat replacements [20–22], whereas preload volume was increased by the addition of water [6]. In this study, preload energy and preload volume were both held constant. Instead, beverage type changed across conditions. This was the first study to directly compare the impact of milk (1% fat), orange juice, and regular cola on hunger, thirst, and satiety, and on energy intakes during a subsequent meal. A carbonated water preload served as a no-energy control condition. The question was whether the three energy-containing beverages would have differential effects on hunger and thirst and on subsequent food consumption or would their effects be substantially the same.

2. Materials and methods

2.1. Participants

Thirty-two participants (14 men and 18 women), ages 18–35 years, were recruited at the University of Washington by means of advertisements and flyers. Enrolled were normal-weight (BMI = 20–27) adults who identified themselves as nondieters, nonsmokers, and regular consumers of breakfast. Potential participants with food allergies or food restrictions, those who disliked two or more foods or beverages in the study; those on prescription medications likely to affect taste, smell, or appetite; athletes in training; and persons reporting recent weight loss or weight cycling were excluded. After a telephone-administered screen to verify eligibility, potential participants reported to the lab for a brief session, during which, their weight and height were measured and recorded. A card stating the dates and times for the study sessions was provided as a reminder. The participants selected for the study attended four sessions, once a week from 9:30 a.m. to 1:00 p.m. To minimize variability within subjects, all participants were asked to report to the lab on the same day of the week if possible, to keep evening meals and activity levels on the day before the test as similar as possible; to refrain from drinking alcohol the day before the test; and to refrain from eating after midnight the day before the test. The study protocol was approved by the Institutional Review Board (IRB) of the University of Washington and all participants provided informed consent. All 32 participants completed the study and were compensated for their time.

2.2. Study design

A within-subjects design was used with each participant returning for four separate test sessions, generally spaced a week apart. The order of presentation of the four beverages was counterbalanced across sessions. The same lunch foods were offered on all four testing occasions. A time interval of 2 h and 15 min between preload and lunch was selected, based on studies showing that a significant change in motivational ratings following a 1500–1600 kJ (375–400 kcal) preload was observed within that time window [17,22]. Power analysis indicated that a sample of 12 subjects, was sufficient to detect a minimum difference of 250 kcal in compensation, with a power of 80% and alpha .05 [23].

2.3. Preload stimuli

The four beverages were orange juice (Minute Maid Original; Coca-Cola, GA); 1% milk (Lucerne; Safeway, CA); cola beverage (Coca-Cola, GA); and carbonated water (Safeway Select Club, Safeway, CA). The beverages were presented chilled but without ice in 591-ml (20-oz) portions in opaque plastic containers with a lid and a straw. Orange juice was prepared by thawing the contents of a can and diluting it with tap water to 1.76 kJ/g (0.42 kcal/g). Energy and nutrient composition of each preload beverage are shown in Table 1. The caloric beverages had the same energy density (1.76 kJ/g or 0.42 kcal/g) and supplied 1036 kJ (248 kcal) each. Participants liked orange juice, cola, and

Table 1
Energy and macronutrient composition of the four beverages

	Orange juice (frozen canned)	1% milk	Cola	Carbonated water
Volume (oz)	20	20	20	20
Energy (kJ)	1036	1036	1036	0
Carbohydrate (g)	61.8	29.1	67.6	0
Total sugars (g)	55.0	28.0	67.6	0
Glucose (g)	27.4	0	25.6	0
Fructose (g)	24.0	0	28.2	0
Lactose (g)	0	28.0	0	0
Fiber (g)	0	0	0	0
Protein (g)	0	20	0	0
Fat (g)	0	6.5	0	0
Energy density (kJ/g)	1.76	1.76	1.76	0

Data from the food label, manufacturer's specifications and from Food Processor software (ESHA, Salem, OR).

1% milk more than sparkling water, as measured by nine-point category scales (described under Motivational ratings section). Preference for orange juice (7.3 ± 0.2), cola (6.4 ± 0.3), and 1% milk (6.2 ± 0.3) were higher than for water (3.9 ± 0.4) [$F(3,28)=25.26$, $P<.001$]. There were no differences in preference ratings by gender. Participants also consumed a standard slice (43 g) of toasted bread (Northwest Eight Grain; Northwest bakeries, WA) for a total of 418 kJ (100 kcal). The bread provided 20 g of carbohydrate, 3 g of protein, and < 1 g of fat.

2.4. Motivational ratings

Participants rated their hunger, thirst, nausea, fullness, and desire to eat, using nine-point category scales. These motivational scales were provided in the form of a booklet, one scale per page. The unipolar adjective scales were anchored at each end with labels "1 = *not at all*" and "9 = *extremely*" [24]. Participants rated each beverage on a number of sensory attributes, using nine-point category scales. They also rated their liking for each beverage along nine-point hedonic preference scales, where "1 = *dislike extremely*" and "9 = *like extremely.*"

2.5. Test meal

A lunch meal was provided at noon. The meal, presented on a tray, included a variety of foods, both savory and sweet. Energy content was 7248 kJ (1734 kcal). Food energy and nutrient values were calculated with the Food Processor software 6.11 (ESHA Research, Salem, OR) and from the manufacturer's food label. Nutrient composition of the bread roll was calculated from the recipe provided by the manufacturer. Nutrient composition of the test meal is shown in Table 2.

Identical meals were provided on each testing occasion. Additional preweighed food portions were available from a self-service buffet and participants were told that they could have as much or as little of any food as they wished. They were asked to record any foods consumed from the side buffet. No caloric beverages were provided as part of the test meal, only still water. All foods were preweighed at the time of serving and plate waste was collected and weighed by the experimenters.

2.6. Procedures

On arrival (9:30 a.m.), participants were seated in separate cubicles in the sensory-evaluation laboratory. They remained there for the duration of the session and were allowed to read, listen to music with earphones, stretch, and use the bathroom. The first set of motivational ratings was obtained on arrival (Time 0). The breakfast preload was served at 9:35 a.m. Participants were asked to consume the breakfast within 25 min and rate the sensory attributes of each beverage. Following ingestion, participants rated the perceived sweetness, aftertaste, and overall liking for the beverage and completed the second set of motivational ratings (Time 1). Additional sets of ratings were completed every 20 min till noon (Times 2–7). After lunch, participants completed the last set of ratings (Time 8) and were given a form to record the foods and beverages they consumed during the rest of the day. The food-record data were not used in the present analyses.

Table 2
Energy and nutrient composition of foods provided at lunch

Food	CHO (g)	Protein (g)	Fat (g)	Sugar (g)	Fiber (g)	Portion	kJ
White-flour roll	48	6.7	0.7	1	1.8	1 roll	957
French mustard	0	0	0	0	0	1 pack	21
Reduced fat provolone cheese	2	18	10	0	0	2 slices	585
Oven-roasted turkey (sliced)	1.2	6.8	0.4	0.8	0	4 slices	167
Honey ham (sliced)	1.2	6.8	1.2	1.2	0	4 slices	167
Salad (spinach leaves with sunflower seeds)	2.8	2	0.8	0	1.9	1.5 cups	377
Fresh large tomato	9.3	1.7	0.7	5.8	2.4	1 piece	176
Fresh fruit (banana, apple or pear)	30.2	0.9	0.7	25	4.3	1 piece	489
Plain-potato chips	32	4	16	0	2	26 chips	1170
Balsamic vinaigrette	4	0	6	3	0	2 tbsp.	293
Light-ranch salad dressing	3	1	7	1	0	2 tbsp.	334
Chocolate-chip cookies	31	2.9	12	14.8	0	4 cookies	1006
Ice cream-sandwich bar	26	3	7	13	0.9	1 bar	752
Fat-free fruit yogurt	38	7	0	35	0	1 yogurt	752
Total grams and energy (kJ)	228.7	60.8	62.5	100.6	13.3		7248

2.7. Data processing and statistics

The Statistical Package for the Social Sciences (SPSS) version 8.0 for Windows [25] was used for data analyses. Analyses of motivational ratings used repeated-measures ANOVA with beverage and time postingestion (Times 1–7) as the within-subjects factors and gender as the between-subjects factor. Analyses of energy and nutrient intakes used repeated-measures ANOVA with beverage as the within-subjects factor and gender as the between-subjects factor. Only when there was a gender interaction, the data were analyzed separately for each group. When appropriate, multiple pairwise comparisons were made adjusting the alpha value with the Bonferroni correction [23]. The strength of the association between cumulative motivational ratings and energy intakes at lunch was tested using Pearson's correlation coefficients. Cumulative ratings were obtained by calculating the area under the curve (AUC) between Time 1 (post-preload) and Time 7 (prelunch).

3. Results

Mean (± S.E.M.) age was 23.1 ± 3.7 years for men and 25.4 ± 4.2 years for women. Mean BMI (kg/m^2) was 23.3 ± 2.0 for men and 22.1 ± 2.1 for women. Participants were Caucasian (75%), Asian (12.5%), and others (12.5%).

3.1. Motivational ratings

As indicated in Fig. 1, hunger ratings were high following an overnight fast, were reduced following preload ingestion (9:45 a.m.), and gradually increased with time. Hunger ratings dropped sharply after lunch. All four breakfasts, regardless of energy content (418 kJ or 1454 kJ), led to a reduction in hunger ratings during the initial 20-min post-ingestion. Analysis of variance of hunger ratings showed a significant main effect of time [$F(6,540)=74.72$, $P<.001$] and of the beverage condition [$F(3,540)=3.84$, $P<.05$], confirming that energy-containing beverages suppressed hunger more effectively than did sparkling water. Multiple pairwise comparisons using Bonferroni correction showed significant differences between water and orange juice ($P<.05$) and marginally, between water and milk ($P=.052$). The three energy-containing beverages were not significantly different from each other ($P>.05$ each). No interaction of the beverage condition with gender was observed [$F(3,540)=0.55$, $P>.05$].

The temporal profile of fullness ratings is shown in Fig. 2. As expected, these data were a mirror image of hunger ratings. Analysis of variance showed main effects of time [$F(6,540)=63.32$, $P<.01$] and beverage condition ($F(3,540)=3.78$, $P<.025$). Multiple pairwise comparisons showed that orange juice and milk were associated with marginally significant higher fullness ratings relative to sparkling water ($P=.05$). There was no significant difference in fullness ratings between cola and other beverages ($P>.05$). There was no interaction of the beverage condition with gender [$F(3,540)=0.98$, $P>.05$].

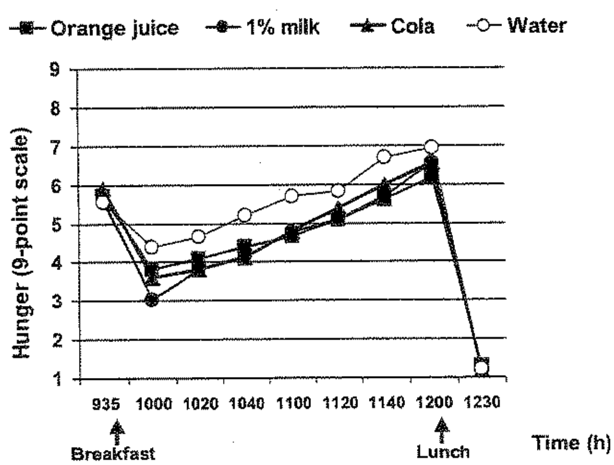

Fig. 1. Temporal profile of hunger ratings as a function of beverage condition ($n=32$).

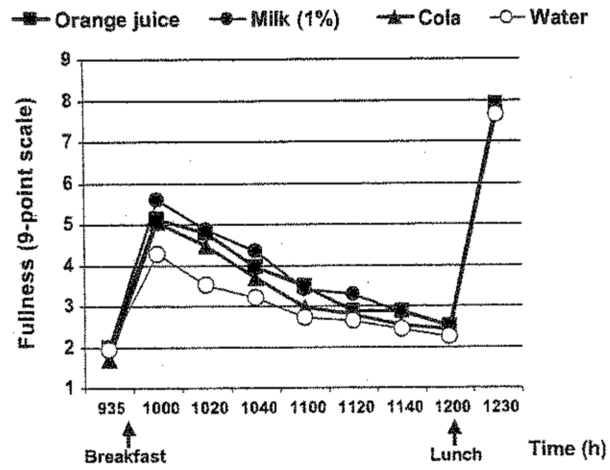

Fig. 2. Temporal profile of fullness ratings as a function of beverage condition ($n=32$).

The temporal profile of thirst ratings is shown in Fig. 3. Although the main effect of time was highly significant [$F(6,540)=47.69$, $P<.001$], the effect of beverage type failed to reach significance [$F(3,540)=2.69$, $P=.05$]. Because thirst ratings showed a small but significant beverage by gender interaction [$F(3,540)=2.97$, $P<.05$], the data were analyzed separately for men and for women. The effect of beverage was significant among women [$F(3,306)=5.05$, $P<.01$] but not among men [$F(3,234)=0.28$, $P>.05$]. Among women, water and orange juice satisfied thirst better than did the cola beverage.

Fig. 4 shows the temporal profile of the desire to eat. Main effects of time [$F(6,540)=66.41$, $P<.001$] and beverage condition [$F(3,540)=4.29$, $P<.01$] were both significant, indicating that the three energy-containing beverages differed from the sparkling-water condition. No differential effect on desire to eat was observed between orange juice and cola, orange juice and milk, or cola and milk ($P>.05$ each). No interaction between beverage type and gender was

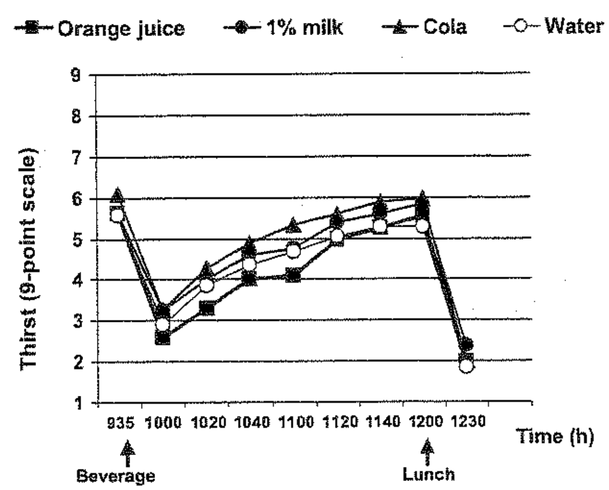

Fig. 3. Temporal profile of thirst ratings as a function of beverage condition ($n=32$).

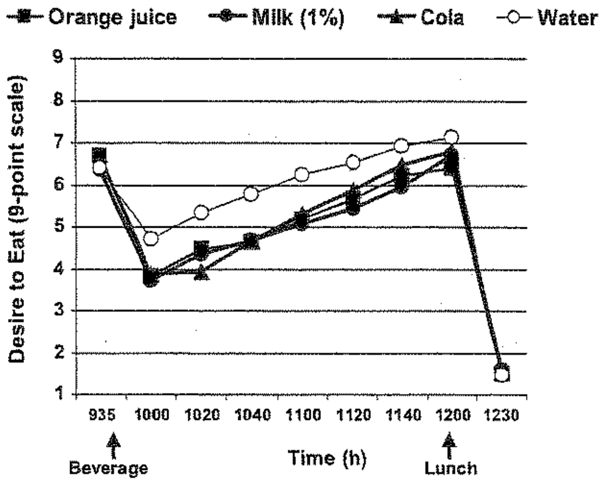

Fig. 4. Temporal profile of the desire to eat as a function beverage condition ($n = 32$).

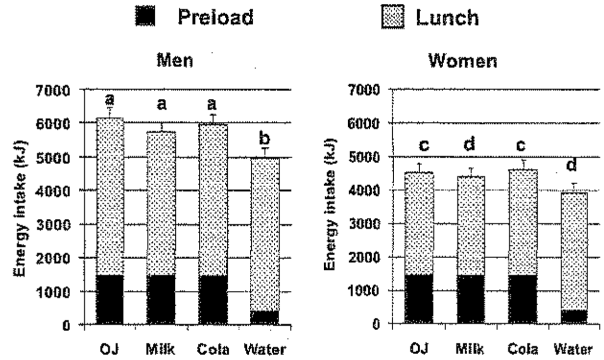

Fig. 5. Total energy intake across conditions including breakfast preload (data are means ± S.E.M.). Within each group, means with different superscript letters are significantly different ($P < .01$).

observed [$F(3,540) = 0.94$, $P > .05$]. Ratings of nausea showed no significant main effect of time [$F(6,25) = 2.19$, $P > .05$] or of beverage condition [$F(3,25) = 0.04$, $P > .05$].

3.2. Energy and nutrient intakes

Energy and nutrient intakes at lunch for each beverage condition are summarized in Table 3, separately for men and women. Mean energy intakes at lunch, exclusive of preload and averaged across conditions, were 4511 ± 151 kJ (1079 ± 36 kcal) for men and 3183 ± 203 kJ (762 ± 48 kcal) for women. Analysis of variance of energy consumed at lunch (exclusive of preload) failed to show a main effect of beverage type [$F(3,90) = 2.47$, $P > .05$].

Total energy intakes, including breakfast preload and lunch, are summarized in Fig. 5. The main effect of beverage type was significant for both men [$F(3,39) = 11.58$, $P < .001$] and women [$F(3,51) = 4.45$, $P < .01$], showing that total energy intakes in the three caloric-beverage conditions were higher than observed for sparkling water. Nutrient composition of the four lunch meals was analyzed separately for men and women. Beverage type had no impact of food selection and did not affect nutrient composition of the meal ($P > .05$). Percent energy from carbohydrate, fat, protein, or sugar was not affected by beverage type ($P > .05$ for all variables).

Cumulative hunger ratings and the desire to eat were related to subsequent energy intakes, but only among women. Analyses of AUC for motivational ratings between Time 1 (post-preload) and Time 7 (prelunch) pooled the data across the four beverage conditions. For women, correlations between hunger and energy intake ($r = .52$; $P < .001$) and desire to eat and energy intake ($r = .59$; $P < .001$) were highly significant. No significant relation between cumulative (AUC) hunger ratings and food consumption at lunch was obtained for men.

4. Discussion

The three energy-containing beverages had comparable effects on satiety, contrary to past suggestions [1]. Using a preload design [10,11,17,20–22], we were able to show that orange juice, low-fat milk (1%), and regular cola had identical temporal profiles for hunger and satiety. The three energy-containing beverages differed from sparkling water, but not from each other, in their effects on hunger, fullness, and desire to eat. The temporal profile of hunger ratings was paralleled by the desire to eat and was the inverse of fullness ratings, consistent with past studies [17,22]. There were no time-related interactions.

The four beverages, including sparkling water, were equally effective in suppressing thirst. No differences in thirst ratings by beverage condition were found among men.

Table 3
Energy and macronutrient consumption after each preload type

	Men ($n = 14$)				Women ($n = 18$)			
	Juice	1% milk	Cola	Water	Juice	1% milk	Cola	Water
Energy (kJ)	4698 ± 288	4277 ± 299	4515 ± 299	4554 ± 311	3080 ± 254	2963 ± 264	3182 ± 264	3509 ± 275
Carbohydrate (g)	150.3 ± 10.1	135.7 ± 9.6	145.2 ± 10.2	143.7 ± 11.2	97.2 ± 8.5	96.3 ± 8.4	102.4 ± 8.3	115.6 ± 7.7
Protein (g)	47.9 ± 1.9	42.2 ± 2.5	43.1 ± 2.9	44.5 ± 2.9	31.0 ± 2.0	30.4 ± 2.4	31.5 ± 2.2	33.7 ± 2.1
Fat (g)	37.5 ± 3.3	35.0 ± 3.7	35.9 ± 3.8	37.7 ± 4.1	24.8 ± 2.9	22.3 ± 2.7	24.7 ± 2.8	27.4 ± 3.2
Sugar (g)	60.7 ± 5.5	51.1 ± 6.0	57.2 ± 5.9	53.7 ± 7.0	38.2 ± 4.0	44.8 ± 4.6	45.2 ± 4.8	48.1 ± 4.4
Total energy (kJ)	6162 ± 303	5746 ± 322	5956 ± 318	4972 ± 354	4537 ± 244	4402 ± 246	4634 ± 247	3927 ± 241

Energy corresponds to that consumed at lunch only (top row) or that from breakfast and lunch (bottom row). Units are mean kJ ± S.E.M.

Among women, water was associated with lower thirst ratings than cola or orange juice. Rolls et al. [20] had reported that water suppressed thirst more effectively than sucrose-sweetened lemonade but in men, however, that effect was not robust and was observed for only one, out of two, volume conditions [20]. The present data provide no evidence for the notion of a differential impact of energy-containing beverages on thirst.

The three energy-containing beverages had the same energy density (1.8 kJ/g) but differed in their nutrient composition, palatability, and sensory profiles. Cola had the highest sugar content and was judged as sweeter than either orange juice or milk. Orange juice and cola had a higher glycemic index (~ 76/100) than did low-fat milk (~ 46/100) [26]. Orange juice, low-fat milk, and cola were all preferred to sparkling water. However, sensory qualities of the energy-containing beverages as well as palatability had no measurable impact on hunger and satiety post-ingestion. The literature on this topic is inconclusive. Sensory factors such as taste, flavor, and texture have been shown to influence satiety in some cases [27–30] but not in others [31].

The lag between the breakfast preload and the test meal was 2.25 h. Differences in motivational ratings between energy-containing beverages and water reached a maximum at approximately 1 h and then converged, consistent with other data [17,22,32]. Beverage type had no impact on subsequent energy intakes or food choices [9,20,32]. Energy intakes at lunch were the same across all four preload conditions and within the range observed for college students in satiety studies [9,12,20,32]. The amount of food provided at lunch was copious (7248 kJ) and all participants had the option to request extra food from a side buffet. As expected, men consumed more energy than did women. However, no significant downward adjustment in energy intake at lunch was observed.

Based on these data, we cannot reject the possibility that the provision of preload energy in liquid form leads to the absence of energy compensation at the next meal. Several researchers have raised the important issue that liquid energy could actually facilitate a positive energy balance and perhaps affect the control of body weight [9,13,14]. However, the focus has always been on energy-containing soft drinks. The present data show that cola beverage was not substantially different in that respect from orange juice or low-fat (1%) milk.

Another possibility is that the 2-h, 15-min time lag between preload ingestion and the test meal was too long for any compensation effect to be observed. Based on what is known about gastric emptying, meals that are largely composed of liquids are rapidly absorbed. A review of the literature suggests that most consistent instances of energy compensation, whether with solid or liquid preloads, were observed in studies with a high preload volume and a very short interval (0–20 min) between the preload and the test meal [7,18–20,27,32–35]. Rolls et al. [6] observed energy compensation in young male subjects following the ingestion of 600 ml of milk-based beverage (2088 kJ and 2.8% fat) given 30 min before lunch. Energy adjustment can also be obscured by high palatability of the test meal [30], so that factor, too, needs to be considered.

In summary, three different energy-containing beverages matched on volume and energy were distinct from sparkling water, but not from each other, in their effects on hunger and satiety. Our data provide no support for the hypothesis that sweetened soft drinks are fundamentally different from orange juice or low-fat milk in their impact on hunger, satiety, and thirst. The present study represents a first direct comparison of common beverages that are regularly used by the consumer.

The data presented here are directly relevant to the current controversy surrounding the role of sweetened beverages in the American diet and their contribution to the rising consumption of high-fructose corn syrup (HFCS) [36–38]. Studies have linked energy-containing beverages with a purported failure of satiety, pointing to little- or no-energy compensation at the subsequent meal, increased energy intake at the long term, and in some cases, weight gain [14]. The present data show that sensory properties and the palatability of the three beverages had little impact on postingestive satiety [39]. As far as satiety was concerned, energy was the important variable. Beverages of the same energy density had comparable effects, and no differential effects on hunger and thirst were observed. Whether liquid and solid foods have the same satiating capacity remains a topic for further study.

Acknowledgements

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High-fructose corn syrup, energy intake, and appetite regulation[1–4]

Kathleen J Melanson, Theodore J Angelopoulos, Von Nguyen, Linda Zukley, Joshua Lowndes, and James M Rippe

ABSTRACT

High-fructose corn syrup (HFCS) has been implicated in excess weight gain through mechanisms seen in some acute feeding studies and by virtue of its abundance in the food supply during years of increasing obesity. Compared with pure glucose, fructose is thought to be associated with insufficient secretion of insulin and leptin and suppression of ghrelin. However, when HFCS is compared with sucrose, the more commonly consumed sweetener, such differences are not apparent, and appetite and energy intake do not differ in the short-term. Longer-term studies on connections between HFCS, potential mechanisms, and body weight have not been conducted. The main objective of this review was to examine collective data on associations between consumption of HFCS and energy balance, with particular focus on energy intake and its regulation. *Am J Clin Nutr* 2008;12(suppl):000.

INTRODUCTION

The effect of caloric sweeteners on body weight remains unclear (1–5). Some studies show inverse relations between intake of sugars and body weight (6–8), whereas others show positive correlations (9–11). Different outcomes may arise from differences in study designs, subjects, liquid versus solid sources of sweeteners, types of sugars studied, and other factors (12). The World Health Organization (13), the US *Dietary Guidelines* (14), and the American Dietetic Association (15) all recommend moderating intakes of total added sugars. However, questions have arisen as to whether certain types of sugars should be limited more than others.

In particular, some experts have implicated high-fructose corn syrup (HFCS) as a possible contributing factor to energy overconsumption, weight gain, and, thus, the rise in the prevalence of obesity over the past decades (9, 16, 17). The purpose of this review was to examine current scientific evidence on HFCS and energy intake regulation in humans to discern whether there may be something inherent about this sweetener that would warrant moderation beyond that of other sweeteners to curb obesity. This review is not intended to refute recommendations by the World Health Organization, the US *Dietary Guidelines*, or the American Dietetic Association regarding moderation of total added sugars in the diet.

HFCS is produced from the isomerization of some of the glucose in corn syrup to fructose. HFCS-55, consisting of 55% fructose and 42% glucose, is used in many sweetened beverages, whereas HFCS-42 (42% fructose; 53% glucose) is used to sweeten other products (eg, confections). Before the mid-1960s, sucrose (50% glucose and 50% fructose) was the predominant sweetener, but food industry developments in the following decades led to increased production of HFCS to replace much of the sucrose (12, 18, 19). HFCS is now estimated to be a major source of fructose in the US diet (3). Although fructose is present in fruit, honey, and some other carbohydrate sources, the quantities consumed from these sources are not as large as is found in foods and beverages sweetened by HFCS.

RELEVANT MECHANISMS OF SUGARS IN THE REGULATION OF APPETITE AND BODY WEIGHT

Postprandial glycemia influences appetite responses to nutrient ingestion either directly or indirectly (20). The glycemic index (GI) values reported for fructose, glucose, and sucrose are considerably different: 19 ± 2, 99 ± 3, and 68 ± 5, respectively (21). The GI of HFCS has not been published, but the GI of cola sweetened with HFCS is 63 ± 5 (21), a figure close to that of sucrose, which might be expected because of the similarities between the sweeteners. Past data have indicated that fructose is more satiating than glucose (22–26). This may have been due, in part, to its low GI; low-GI foods have been associated with greater satiety than high-GI foods (20). Low-GI foods may prolong satiety between meals, whereas high-GI foods may signal immediate satiety (1). Fructose is passively absorbed further down the small intestine than is glucose (27), which may allow prolonged exposure to gastrointestinal satiety signals than higher GI sugars (28). It also imparts high postprandial thermogenic responses and hepatic oxidation (29–33), which may be associated with satiety (34–36).

More recently, fructose's unique metabolism, mainly through energy balance regulatory hormones, has been suggested as a possible mechanism to explain temporal trends in HFCS consumption and obesity (16). Fructose, unlike glucose, does not stimulate insulin secretion from pancreatic β-cells (25). Insulin

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may be a key element in the chain of events that leads to increased satiety with the ingestion of most carbohydrates (37). As a result of high blood glucose, increased circulating insulin can amplify satiety through actions within the central nervous system (37–41) or by stimulating leptin secretion (42). Whereas insulin is secreted in acute response to meals, leptin stimulation is delayed for several hours (43, 44).

Insulin-mediated glucose uptake and metabolism in adipose tissues play a key regulatory role in leptin concentrations (41, 45). Leptin, the diurnal patterns of which have been shown to be regulated by insulin (46), is recognized as a medium- to long-term regulator of energy balance through its effects on reducing energy intake and stimulating energy expenditure (47). Leptin acts via the hypothalamus, blocking the drive to eat caused by energy expenditure from basal metabolism (47) and potentially inhibiting the effects of the orexigenic hormone ghrelin (48–50). It has been suggested that in the case of fructose, which does not stimulate insulin secretion, this chain of satiety-producing events does not occur (16).

Data suggest that the satiating effects of carbohydrates may be mediated through changes in blood glucose, insulin, and carbohydrate utilization (20, 51–57). Secretion of leptin and suppression of ghrelin offer additional potential mechanistic explanations for the satiating effects of carbohydrates (58–60). For example, consumption of high-carbohydrate, low-fat meals results in higher 24-h circulating leptin concentrations in normal-weight women compared with low-carbohydrate, high-fat meals (61). A 12-wk weight reduction study in obese persons showed that a high-carbohydrate (65%), low-fat (15%) diet did not result in the expected weight-loss-induced increases in ghrelin or appetite. This suggests that isocaloric substitution of dietary carbohydrate for fat may lower ghrelin and, thus, hunger (62). Such data may also indicate a role of carbohydrate in ghrelin suppression. Studies show that both oral and intravenous glucose administration lower plasma ghrelin (63, 64). However, fructose consumption does not result in such increases in insulin and leptin secretion or in ghrelin suppression (65). Melanson et al (66) showed that although pure fructose does not increase plasma glucose or insulin, HFCS results in increased plasma glucose and insulin, most likely as a result of the glucose moiety. As discussed below, HFCS and sucrose consumption also produce similar leptin responses and ghrelin suppression (66), as has been seen in other studies in which mixed carbohydrates were fed (67).

Intravenous infusion of glucose does not decrease food intake or visual analogue scale appetite ratings, whereas glucose administered orally or by tube leads to decreased hunger (28). These findings suggest that gastrointestinal factors may mediate carbohydrate-induced satiety. Furthermore, glucose decreases ghrelin secretion and leads to increased glucagon-like peptide-1 (GLP-1) secretion, more so than fructose (68). GLP-1, which is inversely related to ghrelin (69), has an inhibitory effect on food intake through increased satiety (70, 71) and satiation (72).

FRUCTOSE, ENERGY INTAKE, AND ENERGY BALANCE REGULATION

Discrepancies exist between the effects of pure glucose and pure fructose on satiety and energy intake. Some studies show that a glucose preload decreases hunger and inhibits future food intake more than does fructose (73, 74). Others show that fructose inhibits food intake more than does glucose (22–26). Still yet other studies have found no significant differences between the sugars (33, 68, 75–77). A study in 14 healthy men compared 75-g loads of an 80% fructose, 20% glucose mixture (glucose was added to reduce fructose malabsorption), glucose, sucrose and polycose (a branched polymer of glucose often used as a bulking agent), and a sucralose (a calorie-free sweetener) control (78). No significant differences were found in subjective appetite ratings. Ad libitum energy intake at 1 h was suppressed by glucose relative to the sucralose control. Blood glucose correlated with satiety ratings in this study. Intake after the fructose-glucose mixture did not differ significantly from any of the other conditions, including the sucralose condition. Energy intake compensation at the meal 1 h after fructose-glucose consumption was only 11.5% compared with 36–48% from the other beverages. Although this was not statistically significant, it suggests incomplete energy intake compensation.

Inconsistencies in the scientific literature about fructose and energy intake may be related to subjects or the experimental design, eg, the time at which satiety was measured, the amount of carbohydrate given, whether the carbohydrate was as an isolated monosaccharide or was part of a meal, and the route of administration. Lack of difference in energy intake is particularly consistent when fructose is consumed in combination with other carbohydrates (33, 65, 78), which is the case for HFCS and sucrose (**Table 1**). This may be because other carbohydrates influence the speed or completeness of fructose absorption (27) or because energy balance regulatory signals are influenced by the combination of the carbohydrates (66). T1 AQ: 1

Longer-term studies designed specifically to test the effects of pure fructose on energy intake and body weight are extremely limited. An early study in which 14 men with type 2 diabetes supplemented a high-carbohydrate diet with 40–50 g of fructose for 24 wk showed significant weight gain (85). Because total energy intake increased with the fructose supplementation, it is difficult to discern whether the weight gain was specifically related to the fructose. Furthermore, because this study was conducted in persons with diabetes, and there was no control group, applicability to the general population is questionable.

More recently, an outpatient trial was conducted in 7 healthy-weight young males who underwent a 2-wk isocaloric diet that was then supplemented with 1.5 g fructose per kg body wt daily for 4 wk. With each of 3 daily meals, volunteers consumed a 20%-fructose solution. This supplementation resulted in a prescribed excess daily energy intake of 18% from fructose (86). Although total energy intake was not measured, body weight did not change over the 4 wk, suggesting a neutral energy balance despite the added fructose. This could have been due to energy intake compensation or to increased energy expenditure (EE), although 5-h EE, as measured by ventilated hood indirect calorimetry, did not differ significantly throughout the intervention. However, limitations of this study included a lack of a control group, a small sample size, and a short duration.

In terms of fructose and hormonal regulators of energy, fructose tends to blunt insulin responses compared with glucose; these findings are very consistent (33, 65, 68, 77). Although lower GLP-1 responses to fructose have been reported (68), this is not always the case (26, 65, 77). A randomized controlled study in 12 healthy-weight women compared fructose and glucose served in beverages with meals as 30% of total energy intake during two 2-d laboratory visits. On the first day, when the test beverages were included, total energy intake was controlled and

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TABLE 1

Short-term energy intake regulation studies in which fructose was served in the presence of other carbohydrates or in which high-fructose corn syrup was served

Reference	Subjects	Test sweetener	Comparative sweetener	Time frame	VAS	EI	Metabolic responses
Holt et al, 2000 (79)	11 Lean men	Sugared cola	Sugar-free cola	1 d	NS	NS	Not measured
Anderson et al, 2002 (78)	14 Healthy-weight men	80% Fructose, 20% glucose	Glucose, sucrose, polycose	60 min	NS	NS	Blood glucose significantly lower after fructose-glucose than glucose or sucrose
Almiron-Roig and Drewnowski, 2003 (84)	32 Normal-weight adults	HFCS	Orange juice, 1%-fat milk	2 h, 15 min	NS	NS	Not measured
Teff et al, 2004 (65)	12 Normal-weight women	Fructose beverages with meals	Glucose beverages with meals	2 d	NS	NS	Lower blood glucose, insulin, and leptin and less ghrelin suppression after fructose
Wei and Melanson, 2006 (33)[2]	12 Obese men	Fructose milk shakes	Glucose milk shakes	3 h	NS	NS	Lower blood glucose after fructose; higher EE and RQ
Perrigue et al, 2006 (80)[2]	37 Young adults	HFCS-55, HFC-42	Sucrose, 1%-fat milk	140 min	NS	NS	Not measured
Melanson et al, 2007 (66)	30 Normal- weight women	HFCS beverages with meals	Sucrose beverages with meals	2 d	NS	NS	No significant difference in blood glucose, insulin, leptin, or ghrelin suppression
Zuckley et al, 2007 (81)[2]	29 Obese women	HFCS beverages with meals	Sucrose beverages with meals	2 d	NS	NS	No significant difference in blood glucose, insulin, leptin, or ghrelin suppression
Akhavan and Anderson, 2007 (82)	31 Healthy men	HFCS	Sucrose, varied fructose: glucose	75 min (EI @ 80 min)	NS	NS	No significant difference in blood glucose, uric acid, insulin, or ghrelin
Soenen and Westerterp-Plantenga, 2007 (83)	70 Healthy men and women	HFCS	Sucrose (and milk)	120–140 min	NS	NS	No significant difference in blood glucose, GLP-1, insulin, or ghrelin

[1] EE, energy expenditure; EI, energy intake at an ab libitum meal after preload consumption; GLP-1, glucagon-like peptide-1; HFCS, high-fructose corn syrup; NS, not significantly different by statistical analyses; RQ, respiratory quotient; VAS, visual analogue scale ratings of hunger, satiety, and other appetite variables.

[2] Abstract.

subjective appetite was rated. On the second day, the test beverages were not served, and food intake was ad libitum. Results showed that with this large fructose dose, circulating insulin and leptin were lower and postprandial ghrelin suppression was attenuated compared with glucose (65).

After breakfasts served with fructose beverages, ghrelin decreased by ≈50 pg/mL compared with ≈100 pg/mL after glucose. Although postprandial peaks in the active form of GLP-1 were similar after meals served with fructose-sweetened versus glucose-sweetened beverages, active GLP-1 remained higher after lunch and dinner during the fructose trials compared with the glucose trials. Despite hormonal differences, subjective appetite and ad libitum energy intake did not differ between fructose and glucose conditions in this study. However, in the 5 women with high scores for dietary restraint (measured by the Three-Factor Eating Questionnaire), higher hunger and fat intake were seen in the fructose condition. Although these women did not have different hormonal responses, potential susceptibility to fructose according to subject characteristics should be followed up in larger groups of persons. This study would need to be followed up over longer periods to determine whether these differences in hormonal, but not overall appetitive responses, persist with time.

HIGH-FRUCTOSE CORN SYRUP, ENERGY INTAKE, AND BODY WEIGHT: SHORT-TERM STUDIES

The study noted above (65), compared beverages sweetened with pure fructose and glucose, but as described earlier, HFCS is more similar to sucrose than it is to fructose. Thus, although the above study provides evidence that excess fructose consumption can be detrimental to metabolism, it did not address the issue of whether the replacement of sucrose in the American diet with HFCS may be problematic. Therefore, Melanson et al (66) conducted a similar study design with two 2-d visits in 30 healthy-weight young women to compare hormonal and appetitive responses to beverages sweetened by HFCS or sucrose. The beverages were served with 3 meals during the day and provided 30% of energy intake. As with the previous study, energy intake was controlled on the first day when the test beverages were served and appetite was rated, and food intake was ad libitum on the second day of each visit.

Blood glucose, insulin, leptin, and ghrelin did not differ significantly between the 2 sweeteners. HFCS- and sucrose-sweetened beverages produced similar ghrelin suppression after each meal of ≈200 pg/mL after both sucrose and HFCS trials. As was seen in the fructose-glucose study described above (65), no significant differences were seen between HFCS and sucrose in ad libitum energy or macronutrient intakes. Appetite ratings were also similar (the one exception was a slightly greater desire to eat after sucrose consumption). Lack of differences between HFCS and sucrose in energy intake and appetite ratings are not surprising because of similar responses in plasma glucose, insulin, leptin, and ghrelin (66), all of which have been postulated as biomarkers of energy intake regulation (36).

Zuckley et al (81) recently repeated the same study design to compare hormonal and appetitive responses to HFCS and sucrose in obese and overweight women. As with the previous study, preliminary findings showed that these responses to HFCS and sucrose do not differ significantly in persons carrying excess body weight. Similar blood glucose and hormones, as well as appetite ratings and ad libitum energy intake, were seen with consumption of HFCS and sucrose. Such results should be explored in other populations, eg, obese men and older, and younger persons. Additionally, total dietary HFCS should be differentiated from beverage sources of HFCS, and outcomes beyond these 3 hormones and appetite should be measured.

Two recent publications, each reporting 2 short-term experiments, have corroborated data showing a lack of differential hormonal and appetite responses to HFCS and sucrose (82, 83). In a total of 31 healthy subjects across 2 experiments, no differences between the sweeteners were seen in acute (75–80 min) responses of appetite, blood glucose, uric acid, insulin, and ghrelin ($n = 7$ for these 3 last variables) (82). Preloads of HFCS, sucrose, or milk produced similar 2-h responses of glucose, insulin, GLP-1, ghrelin, rated appetite, and energy intake compensation in a total of 70 healthy men and women across 2 experiments (83).

Appetite responses to beverages sweetened by HFCS have been compared with a variety of other beverages. For example, in a study of 14 men and 18 women who served as their own controls, isovolumetric 248-kcal drinks were served with a slice of toast, and an ad libitum lunch was served 2 h and 15 min later (84). The drinks were tested in random order on separate days, including HFCS-sweetened cola, orange juice, and 1%-fat milk. These were compared with isovolumetric carbonated water. Although the 3 energy-containing beverages suppressed subjective hunger ratings, desire to eat, and ad libitum intake more than did water, they did not differ significantly from each other.

Similar results were seen in a preliminary study that compared cola sweetened with sucrose, HFCS-55, HFCS-42, or aspartame; 1%-fat milk; and a no-beverage control in 37 adults in a randomized paired design (79). Hunger and satiety ratings did not differ significantly among the beverage treatments. Relative to the 2 no-energy treatments, energy intake compensation was similar among the 4 energy-containing drinks at the meal 140 min later. These 2 studies examined typical HFCS loads and found similar appetite responses compared with isocaloric beverages. Therefore, it is possible that the fructose content of typical HFCS loads may be below the fructose threshold required to alter metabolism, or that the presence of other carbohydrate sources might prevent metabolic alterations. These possibilities warrant further investigation.

Eleven healthy young males participated in a randomized study to compare appetite after consumption of isovolumetric preloads of sugar-rich cola, sugar-free cola, and mineral water on separate days (80). The sweetener of the sugar-rich cola was not clarified in this study, but because it took place in Australia, it is possible that the sweetener was sucrose rather than HFCS. However, the results showed that satiety immediately after the preloads was more dependent on volume than on energy content or sweetness. Lunch intake after the preloads suggested insufficient energy intake compensation for the energy in the sugar-rich cola, although this was not statistically significant. Total energy intake over the full day did not differ among the preloads, which suggests that, with time, energy intake evened out.

HIGH-FRUCTOSE CORN SYRUP, ENERGY INTAKE, AND BODY WEIGHT: LONGER-TERM STUDIES

On the basis of studies focused specifically on fluids, high consumption of sugar-sweetened beverages, in general, may be associated with excess body weight (87). Drinking soda sweetened with HFCS has been associated with increased ad libitum energy intake and body weight compared with the same amount of soda sweetened with the noncaloric sweetener aspartame (10). Studies have also shown increases in energy intake and body weight over 10 wk when subjects incorporated sucrose, as compared with nonnutritive sweeteners, into their diets (11). In children, Ludwig et al (9) found that the overall quantity of sugar-sweetened beverages ingested was predictive of initial and follow-up body mass index. Prospective epidemiologic data in adults have associated increases in sugar-sweetened beverages with weight gain (88). Together, these studies imply that increased energy intake by sweetened beverages is not compensated for in subsequent intake, which may lead to overconsumption. However, these studies do not determine whether HFCS may be more of a factor in weight gain than other caloric sweeteners, nor do they specifically address the implications of total dietary HFCS from all sources on energy intake and body weight. Overall, longer-term studies have mainly compared HFCS with noncaloric sweeteners; prospective studies comparing HFCS with other caloric sweeteners are needed.

Most studies of HFCS, energy intake, and body weight have specifically focused on beverage consumption rather than total dietary HFCS. Some research has shown that energy intake compensation is less precise when caloric beverages are consumed versus solid food (1, 89, 90). For example, a study that compared weight gain after 4 wk of consumption of a sweetened soda versus the same carbohydrate load in the form of jelly beans found more weight gain after the beverage (90). However, a recent review (91) provided evidence that questions the plausibly of claims that liquid energy sources, in particular, may increase weight gain. For example, because liquid meal replacements can promote weight loss when used appropriately, appropriate use of caloric beverages (ie, replacing calories versus adding calories) may be more of a concern.

CONCLUSIONS

Collectively, scientific evidence suggests that high consumption of pure fructose may be problematic to energy intake regulation. However, HFCS is more similar to sucrose than it is to fructose in terms of its content, appetitive responses, and aspects of its metabolism that have been measured to date. Thus, existing theoretical and empirical evidence suggests that fructose-induced problems are not relevant to HFCS consumption.

The potential hormonal and physiologic responses to HFCS have not yet been connected to longer-term appetite or metabolism, and, thus, to body weight regulation. Longer-term studies have mainly compared HFCS beverages with noncaloric beverages, and, therefore, are relevant more to the issue of increased caloric intake from sweeteners than to the effects of specific
AQ: 2 sweeteners relative to each other. Research is needed in this area, especially considering the significant use of sweeteners in the United States and other developed countries (3, 12, 18, 19). It is important to determine whether any sweetener needs to be limited more than others. Mechanistic approaches, as well as outcome-oriented approaches focused on energy intake and body weight, should be included in this research agenda.

As shown in Table 1, insufficient scientific evidence currently exists to indicate that HFCS disrupts short-term energy balance signals or increases short-term appetite and energy intake more than do other sweeteners. The metabolic and endocrine responses that have been measured to date are similar between HFCS and sucrose, the sweetener HFCS has largely replaced in the US diet. Additional work should be performed to see whether these results extend to other metabolic and endocrine responses. In addition, longer-term investigations of the effect of HFCS on energy balance regulatory systems are needed to further understand the role of this sweetener in body weight regulation.

Other articles in this supplement to the Journal include references 92-95.

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No differences in satiety or energy intake after high-fructose corn syrup, sucrose, or milk preloads[1–3]

Stijn Soenen and Margriet S Westerterp-Plantenga

ABSTRACT

Background: It is unclear whether energy-containing drinks, especially those sweetened with high-fructose corn syrup (HFCS), promote positive energy balance and thereby play a role in the development of obesity.

Objective: The objective was to examine the satiating effects of HFCS and sucrose in comparison with milk and a diet drink.

Design: The effects of 4800-mL drinks containing no energy or 1.5 MJ from sucrose, HFCS, or milk on satiety were assessed, first in 15 men and 15 women with a mean (±SD) body mass index (BMI; in kg/m^2) of 22.1 ± 1.9 according to visual analogue scales (VAS) and blood variables and second in 20 men and 20 women (BMI: 22.4 ± 2.1) according to ingestion of a standardized ad libitum meal (granola cereal + yogurt, 10.1 kJ/g).

Results: Fifty minutes after consumption of the 1.5-MJ preload drinks containing sucrose, HFCS, or milk, 170%-mm VAS changes in satiety were observed. Glucagon-like peptide 1 (GLP-1) ($P < 0.001$) and ghrelin ($P < 0.05$) concentrations changed accordingly. Compensatory energy intake did not differ significantly between the 3 preloads and ranged from 30% to 45%. Energy intake compensations were related to satiety ($r = 0.35$, $P < 0.05$). No differences were observed between the effects of the sucrose- and HFCS-containing drinks on changes in VAS and on insulin, glucose, GLP-1, and ghrelin concentrations. Changes in appetite VAS ratings were a function of changes in GLP-1, ghrelin, insulin, and glucose concentrations.

Conclusion: Energy balance consequences of HFCS-sweetened soft drinks are not different from those of other isoenergetic drinks, eg, a sucrose-drink or milk. *Am J Clin Nutr* 2007;86:1586–94.

KEY WORDS Glucagon-like peptide 1, ghrelin, insulin, glucose, energy intake

INTRODUCTION

Trends in overweight are consistent with increased energy intake over recent decades (1). The upward shift in energy intake may partly consist of the consumption of soft drinks (2–5). Increased soft drink consumption has coincided with the increase in prevalence of overweight and obesity (6, 7) over the past 3 decades in the United States (8–10). In the 1970s, the food industry in the United States introduced high-fructose corn syrup (HFCS) sweetener as a substitute for sucrose (11). It has been suggested that the obesity epidemic may have been aggravated by the increase in HFCS consumption (12).

Drinking HFCS-sweetened soda was reported to increase energy intake and body weight (13). However, several studies have reported that fructose, when consumed alone, reduced subsequent energy intake equally in some (14–16) or significantly more in other studies (17–19) compared with a monosaccharide glucose preload. Yet, it should be noted that the principal sweetener in soft drinks in the United States, HFCS, is not pure fructose but a mixture of fructose (55%) and glucose (45%). Factors that may account for the different effects of fructose alone or a mix of fructose and glucose are its gastrointestinal effects and absorption characteristics (20, 21).

In addition to the composition of ingested carbohydrates, the physical state of intake may be important in influencing subsequent energy intake compensation. Compensatory dietary responses to energy-containing beverages have been found to be less precise than those to isoenergetic solid loads (22, 23). Thus, fluid carbohydrates such as soft drinks could increase the risk of excess total energy intake. An effect of soft drink consumption, eg, of sucrose compared with artificial sweeteners, on weight gain and obesity has been found in children (24–26), adolescents (27), and adults (28, 29). On the basis of these studies, it is suggested that carbohydrates in liquid form promote a positive energy balance and therefore contribute to the development of obesity.

Compensation for energy intake from drinks by a change in energy intake at the subsequent meal depends on the moment in

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TABLE 1
Subject characteristics

	Study 1		Study 2		
	Women (n = 15)	Men (n = 15)	Women (n = 20)	Men (n = 20)	P (ANOVA)[1]
Age (y)	21.1 ± 1.5 (7)[2]	21.5 ± 1.8 (8)	21.2 ± 2.2 (10)	22.3 ± 4.5 (20)	
Weight (kg)	63.7 ± 7.3 (12)	75.8 ± 9.5 (13)	65.0 ± 7.7 (12)	76.2 ± 6.0 (8)	<0.001
Height (cm)	171.4 ± 5.6 (3)	183.3 ± 8.0 (4)	171.6 ± 4.6 (3)	183.0 ± 7.2 (4)	<0.001
BMI (kg/m^2)	21.6 ± 1.9 (9)	22.5 ± 1.8 (8)	22.0 ± 2.1 (10)	22.8 ± 2.0 (9)	
Systolic blood pressure (mm Hg)	123 ± 14 (11)	131 ± 11 (8)	123 ± 11 (9)	130 ± 10 (8)	<0.05
Diastolic blood pressure (mm Hg)	73 ± 9 (12)	78 ± 10 (13)	74 ± 8 (11)	77 ± 7 (9)	
F1, cognitive restraint[3]	5.1 ± 2.9 (57)	3.3 ± 2.2 (67)	5.5 ± 3.0 (55)	3.3 ± 2.1 (64)	<0.005
F2, disinhibition[4]	4.9 ± 1.9 (39)	3.1 ± 1.1 (35)	5.0 ± 2.0 (40)	4.0 ± 2.0 (50)	<0.01
F3, hunger[5]	4.5 ± 2.9 (64)	3.3 ± 1.8 (55)	4.4 ± 2.9 (66)	5.1 ± 3.4 (67)	
Insulin (mU/L)[6]	12.9 ± 4.1 (32)	12.7 ± 3.8 (30)			
Glucose (mmol/L)[6]	4.9 ± 0.3 (6)	5.3 ± 0.4 (8)			<0.001

[1] Represents differences between men and women; all subjects participated in either study 1 or 2 (n = 57; 13 subjects participated in both studies).
[2] $\bar{x}$ ± SD; CV in parentheses (all such values).
[3] A measure of cognitive restraint with the Three-Factor Eating Questionnaire (TFEQ); minimum score = 0, maximum score = 21; cutoff point for the Dutch population was 9. Values >9 indicate cognitive restraint eating.
[4] A measure of disinhibition or emotional eating with the TFEQ; minimum score = 0, maximum score = 14.
[5] A general feeling of hunger with the TFEQ; minimum score = 0, maximum score = 14.
[6] Average plasma concentrations over the 4 test days after the subjects fasted overnight.

time of preload ingestion. Time delay between preload and test meal interferes with the outcome of preload studies (30–32).

The objective of the present study was to examine whether there is a difference in response between a HFCS-sweetened and a sucrose-sweetened isoenergetic, isovolumetric orange-flavored preload and a no-energy control. A milk preload was used to compare the soft drinks with another type of liquid preload. In the first study, the responses were measured as the appetite profile using visual analogue scales (VAS) and as a possible change in the satiety hormones: glucagon-like peptide 1 (GLP-1), insulin, ghrelin, and glucose. Moreover, the latest time point after ingestion when relevant differences in satiety scores or satiety hormone concentrations were still present was determined as the moment in time for the subsequent test meal. In the second study, possible compensation in energy intake during an ad libitum subsequent meal was determined. The studies were conducted in Europe, so subjects had a negligible history of consuming HFCS-containing products.

SUBJECTS AND METHODS

Subjects

Subjects were recruited by means of an advertisement in local newspapers and on notice boards at Maastricht University. Subjects who were willing to participate in the study were subsequently screened by means of a detailed medical history and a physical examination. All subjects were in good health, were normotensive, were nonsmokers, were nonrestrained eaters, were regular breakfast consumers, were at most moderate alcohol users, had a stable body weight (a change of <2 kg over at least the past 2 mo) and did not use prescription medication. Excluded from the study were athletes, defined as those who trained >10 h/week. Thirty subjects (equal numbers of men and women) participated in the first study, 40 in the second study. Subject characteristics are given in **Table 1**. Subjects were requested to maintain their customary level of physical activity and normal dietary habits and not to gain or lose weight for the duration of the study. All subjects gave written informed consent, and the experimental protocol was approved by the local Medical Ethics Committee of the University of Maastricht, Maastricht, Netherlands.

Study design

A within-subjects design was used, with each subject returning for 4 separate test days ≥1 wk apart. The preloads were offered blindly and in randomized order to avoid the order-of-treatment effect. To analyze possible differences in the appetite profile, VAS ratings and blood samples for the measurement of GLP-1, ghrelin, insulin, and glucose concentrations were collected before and after preload consumption in the first study. The last moment in time at which relevant differences in satiety were present was determined to decide on the timing of the test meal in the second study. The second study consisted of the same preload consumptions as in the first study, with VAS ratings of the appetite profile before and after the preload and a test meal at the relevant moment in time, as defined by the first study.

Anthropometric measures

Body weight was determined during screening and on each test day with a digital balance (weighing accuracy of 0.02 kg; Chyo-MW-150K; Chyo, Japan) while the subjects were wearing underwear and in a fasted state and after they had emptied their bladders. Height was measured to the nearest 0.1 cm with a wall-mounted stadiometer (model 220; Seca, Hamburg, Germany). Body mass index (BMI) was calculated by dividing body weight (kg) by height squared (m^2). Systolic and diastolic blood pressures were recorded during screening with an automatic blood pressure monitor (OSZ 5 easy; Spreidel & Keller GmBH and Co, KG, Jungingen, Germany).

TABLE 2
Energy and macronutrient composition of the 4 preloads and the meal[1]

	Preload				
	Sucrose-containing preload[2]	HFCS-containing preload[3]	Milk preload	Diet preload	Meal[4]
Carbohydrate [kJ (%)]	1500	1500	632	0	554 (55)
Glucose [kJ (%)]	960 (64)	615 (41)	0	0	
Fructose [kJ (%)]	540 (36)	885 (59)	0	0	
Lactose [kJ (%)]	0	0	632 (42)		
Protein [kJ (%)]	0	0	442 (30)	2	80 (8)
Fat [kJ (%)]	0	0	426 (28)	0	378 (37)
Energy (kJ)	1500	1500	1500	2	1012
Volume (mL)	800	800	800	800	
Energy density (kJ/g)	1.9	1.9	1.9	0	10.1

[1] HFCS, high-fructose corn syrup. Values reported as percentages represent the percentage of energy of the energy-containing macronutrients.
[2] 66% sucrose and 34% glucose syrup (91% glucose and 9% fructose).
[3] 55% fructose and 45% glucose syrup (91% glucose and 9% fructose).
[4] The test meal consisted of a granola cereal and yogurt; values are expressed per 100 g.

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Preloads

The 4 beverages were as follows: a beverage containing sucrose, one containing HFCS, one containing milk, and a diet drink. The energy content and macronutrient composition of the 4 beverages are specified in **Table 2**. All 4 drinks were isovolumetric and had a volume of 800 mL. The energy drinks were isoenergetic and provided 1.5 MJ. The diet drink had an energy content of 0.2 MJ. The drinks containing sucrose or HFCS and the diet drink were orange-flavored custom-made beverages and were equally sweet. The sucrose-containing preload had the same consistency as a commercially available sucrose-sweetened drink containing 450 g sucrose and 236 g glucose syrup (91% glucose and 9% fructose). The HFCS-containing preload had the consistency of a commercially available HFCS-sweetened drink containing 55% fructose and 45% glucose syrup (91% glucose and 9% fructose). The diet preload consisted of the sweeteners aspartame, acesulfame-K, and sodium cyclamate. Additionally, all 3 preloads contained water, citric acid, orange flavoring, coloring E160, preservative E202, and antioxidant E300. Drinks were prepared by diluting 133 mL syrup with 667 mL water. All 4 beverages were served chilled at 8 °C.

Test meal

The test meal that was served in the second study consisted of a granola cereal with yogurt. The nutrient composition of the test meal is shown in Table 2. Subjects were requested to continue eating until they felt comfortably full. All foods were preweighed at the time of serving, and plate waste was collected and weighed.

Attitude toward eating

The subjects' attitude toward eating was determined during screening with the use of a validated Dutch translation of the Three-Factor Eating Questionnaire (TFEQ) (33, 34). The scores on cognitive restrained and unrestrained eating behavior (F1), emotional eating and disinhibition of control (F2), and subjective feeling of hunger (F3) are shown in Table 1.

Appetite profile

The subjects' feelings of hunger, satiety, fullness, prospective food and drink consumption, and desire to eat and drink were scored on anchored 100-mm VAS at 6 different 0.5-h time points in study 1 and at 7 time points in study 2. The scale ranged from "not at all" on the left to "extremely" on the right. Subjects were instructed to mark, with a single vertical line, a point where the length of the line matched their subjective sensation. All VASs were provided on a separate form at each time point and were collected immediately after they had been completed.

Taste perception and hedonics

Subjects rated their taste perception and hedonics for the 4 test drinks on anchored 100-mm VAS during screening and at the first and last sip of the beverage consumed during each test day (**Table 3**). The following scales had to be completed: how sweet, sour, bitter, or salty the drink was; how rich, creamy, and fresh the flavor of the drink was; and how pleasant the drink was in the mouth.

Blood samples

Venous blood samples were taken at 5 time points: one fasting sample at baseline before and 4 samples 15, 30, 60, and 120 min after preload consumption. After each blood collection, the intravenous cannula was rinsed with 0.9% sterile sodium chloride solution containing 1% heparin. Blood samples were taken to determine concentrations of plasma GLP-1, ghrelin, insulin, and glucose. The

TABLE 3
Perception of taste characteristics[1]

	Sucrose-containing preload	HFCS-containing preload	Milk preload	Diet preload
Sweetness	66 ± 14[a]	70 ± 17[a]	25 ± 22[b]	52 ± 22[c]
Sourness	20 ± 20[a,b]	29 ± 23[a,c]	13 ± 16[b]	37 ± 21[c]
Bitterness	12 ± 12[a]	15 ± 17[a,c]	12 ± 17[a,b]	23 ± 21[c]
Saltiness	8 ± 10[a]	8 ± 12[a]	10 ± 15[a]	14 ± 17[a]
Richness	44 ± 23[a]	50 ± 24[a]	68 ± 16[b]	41 ± 25[a]
Creaminess	13 ± 16[a]	14 ± 14[a]	77 ± 13[b]	13 ± 15[a]
Refreshing	67 ± 14[a]	66 ± 14[a]	41 ± 20[b]	61 ± 19[a]
Pleasantness	70 ± 14[a]	68 ± 15[a]	52 ± 21[b]	50 ± 23[b]
Intenseness	51 ± 19[a]	59 ± 21[a]	50 ± 26[a]	48 ± 22[a]

[1] All values are $\bar{x}$ ± SD. HFCS, high-fructose corn syrup. Means in a row with different superscript letters are significantly different, $P < 0.05$ (ANOVA).

blood samples were collected in tubes containing EDTA to prevent clotting. Blood samples for GLP-1 analysis were collected in ice-chilled syringes containing 20 μL dipeptidyl peptidase-IV (DPP-IV) inhibitor (Linco Research Inc, St Charles, MO) to prevent degradation. Plasma was obtained by centrifugation (1500 $\times$ g, 10 min, 4 °C), frozen in liquid nitrogen, and stored at −80 °C until analyzed. Plasma ghrelin samples were mixed with hydrochloric acid, methanol, and phenylmethanesulfonyl fluoride (Sigma-Aldrich, Zwijndrecht, Netherlands). Plasma concentrations of active ghrelin were measured by radioimmunoassay (Linco Research Inc) and those of active GLP-1 by enzyme-linked immunosorbent assay (EGLP-35K; Linco Research Inc). Insulin samples were analyzed with a radioimmunoassay kit (Linco Research Inc), and glucose samples were measured by using a hexokinase method (ABX Diagnostics, Montpellier, France).

Test day procedure

After fasting overnight, the subjects arrived at the laboratory at 0815. The subjects were asked to consume their habitual evening meals, to refrain from alcohol or strenuous exercise, and to refrain from eating and drinking after 2300 on the day before each test. Body weight was measured, and an intravenous Venflon cannula (Baxter BV, Utrecht, Netherlands) was inserted in the antecubital vein to enable blood sampling (study 1). The subjects remained seated in comfortable chairs separated by large room dividers with minimal disturbance from the investigators throughout the experimental session. During each test day, the subjects were isolated from time cues to eliminate as much as possible habitual (time-determined) meal patterns; no watches, clocks, or radios were present in the test room, and the research refrained from making time-related statements. The subjects were allowed to stretch their legs, use the bathroom, read, listen to music, or watch movies, but not while drinking the preload or eating the meal (study 2). At 0900, after collection of the baseline appetite profile and blood sample, the subjects received 1 of the 4 liquid preloads. The preloads had to be consumed entirely within 10 min. The preloads were accompanied by a VAS of taste perception and hedonics at the first and last sips of the beverage. Blood sampling in study 1 was repeated 15, 30, 60, and 120 min after preload consumption and the appetite profile 20, 50, 80, 110, and 140 (last time point only in study 2) min after preload consumption. The catheter was removed after the last blood sample had been taken. The meal in study 2 was served 50 min after preload consumption based on the VAS ratings or differences in increases of satiety hormones in the first study.

Statistical analysis

Data are presented as means ± SDs or SEs. VAS ratings were measured in millimeters from the left end of the scale. The changes in concentrations of the hormones from baseline and changes from baseline in VAS ratings of the appetite profile were compared by analysis of variance (ANOVA), repeated-measures ANOVA (analysis of change score), and analysis of covariance (ANCOVA) with the baseline values as covariates. Because the experiment was fully randomized with a 1 wk washout between the tests, because there was no significant difference between the baseline scores, and because the washout period was longer than the actual experiment, it is more appropriate to use the analysis of change score from baseline with an n-factor repeated-measures ANOVA instead of ANCOVA (35). An ANCOVA may give bias because of the "weight" of the baseline values (35). Post hoc analysis was carried out with a Fisher's protected least-significant difference test, Sheffe's F test, or a Tukey's test. Taste perception and energy intake after the preloads were compared by ANOVA. Differences in responses between the drinks containing sucrose and HFCS were compared with a 2-tailed paired Student's t test. Sex differences were assessed by using ANOVA. Time-by-sex interactions were assessed by using repeated-measures ANOVA, and time-by-treatment-by sex interactions were assessed by using multivariate ANOVA with preload condition and sex as fixed factors. Changes in the desire to eat from baseline were analyzed as a function of changes in concentrations of hormones and glucose from baseline by regression analysis. Compensation was calculated as the difference between energy intake after the diet preload and energy intake after any of the energy preloads as a percentage of the energy content of these preloads. Overconsumption was calculated as a difference between total energy intake after any of the energy preloads and total energy intake after the diet preload as a percentage of energy intake after the diet preload. All analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 11.0.3 for Macintosh OS X (SPSS Inc, Chicago, IL). Differences were regarded as significant if $P < 0.05$.

RESULTS

Perception of taste characteristics

Drinks containing sucrose or HFCS (800 mL, 1.5 MJ) did not differ in taste perception or palatability. The milk preload (800 mL, 1.5 MJ) was perceived as less sweet, sour, refreshing, and pleasant ($P < 0.01$) and more rich and creamy than the preloads containing sucrose or HFCS ($P < 0.005$). The diet preload (800 mL, 2 kJ) was perceived as less pleasant and less sweet than preloads containing sucrose or HFCS ($P < 0.001$) (Table 3). Taste perception did not differ between sexes. Perceptions of thirst after the preloads did not differ between the preloads. Thirst was significantly more reduced in women than in men [change in area under the curve (AUC) from baseline: −18 ± 9 compared with −31 ± 16 mm VAS/min respectively; $P < 0.05$].

Determination of the moment in time to serve the test meal in study 2

In study 1 we determined the moment in time to serve the meal in study 2. The right moment was determined by identifying the moment in time when the mean difference in responses to the preloads containing sucrose or HFCS was statistically significant. This moment appeared to be 50 min after the preload consumption. This moment in time was underscored by the following. Although preloads containing sucrose or HFCS did not differ in satiety and hunger ratings in the total group (**Figure 1**), the reduction in hunger relative to baseline after a preload differed significantly between men and women ($P < 0.05$). Men had a significantly greater reduction in hunger after the preload containing HFCS than after the preload containing sucrose at the 50-min time point (−8 ± 14 compared with −17 ± 15 mm VAS, respectively; $P < 0.05$), whereas women showed the opposite. Women had a significantly greater reduction in hunger ratings at the 50-, 80-, and 110-min time points, with the maximal difference occurring 50 min (−24 ± 18 compared with −7 ± 19 mm VAS; $P < 0.05$) after consumption of

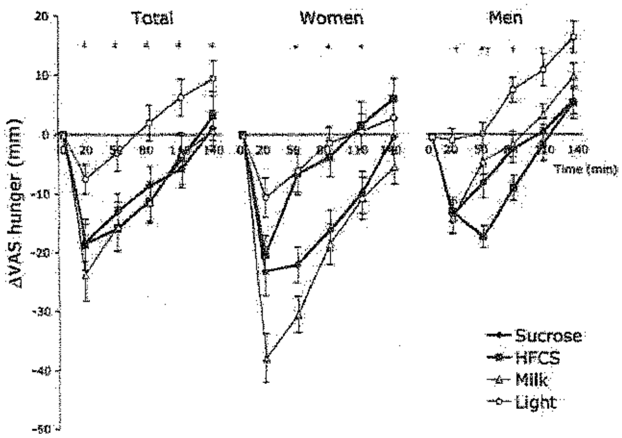

FIGURE 1. Mean (±SEM) change (Δ) in hunger of the total group (n = 30) and in men (n = 15) and women (n = 15) separately as a function of preload condition (study 1). There was a significant time-by-treatment-by-sex interaction, $P < 0.05$ (multivariate ANOVA). ‡Significant difference between the diet preload and the sucrose- and high-fructose corn syrup (HFCS)–containing preloads and the milk preload, $P < 0.05$ (repeated-measures ANOVA). †Significant difference between the diet preload and the sucrose- and HFCS-containing preloads, $P < 0.005$ (ANOVA). *Significant difference between the sucrose- and HFCS-containing preloads, $P < 0.05$ (2-tailed paired Student's t test).

the preload containing sucrose compared with the preload containing HFCS. Thus, the adequate moment in time to serve the test meal in study 2 was 50 min, as underscored by the significant treatment-by-sex interaction at 50 min ($P < 0.05$). Differences in VAS ratings between treatments differed by sex. This moment in time was not supported by differences in concentrations in GLP-1, ghrelin, insulin, or glucose relative to baseline, as illustrated in **Figure 2**. However, changes in VAS ratings relative to baseline were a function of changes in concentrations of the hormones GLP-1, ghrelin, and insulin relative to baseline values (**Table 4**). Stepwise multiple linear regression analysis of VAS appetite ratings showed that change in GLP-1 ($r = -0.242, P = 0.014$) and insulin ($r = -0.239$, $P = 0.029$) independently predicted changes in satiety. Moreover, glucose and insulin concentrations were related after preload consumption, as expected, and GLP-1 and ghrelin concentrations were related to insulin concentrations. GLP-1 and ghrelin concentrations were not related to each other (Table 4). Furthermore, the determination of the adequate moment in time to serve the meal in study 2 was underscored by the decrease in glucose concentrations (Figure 2).

Energy-containing preloads compared with the diet preload

Meal size and energy intake were significantly lower after consumption of preloads containing sucrose or HFCS or the milk preload than after the diet preload (**Table 5**). This finding was supported by the significantly higher GLP-1 and insulin concentrations (Figure 2; $P < 0.001$) and the significantly lower ghrelin concentrations (Figure 2; $P < 0.05$) and hunger (Figure 1; $P < 0.05$) after the energy-containing preloads than after the diet preload. Thus, less energy was consumed after consumption of an energy drink than after a drink designed to not deliver energy. Total energy intake (preload + meal) with the energy-containing preloads was significantly higher than total energy intake with the diet preload (Table 5). Therefore, during the meal, energy intake was only partly compensated for. Compensation for energy intake from the preloads containing sucrose, HFCS, or milk did not differ significantly (Table 5) and ranged from 30% to 45%. Energy consumed after preloads, compensation, and overconsumption differed significantly between men and women ($P < 0.01$). This sex difference was supported by the significant time-by-sex interactions for glucose and GLP-1 concentrations ($P < 0.01$). Compared with women, men had lower GLP-1 concentrations at baseline ($P < 0.05$) and a smaller change in GLP-1 concentration from baseline after preload consumption ($P < 0.01$). Appetite ratings after drink consumption decreased significantly more in women than in men ($P < 0.05$). Decreases in hunger scores were not different between the 4 conditions after ingestion of the meals.

Compensation after the energy-containing preloads was a function of the magnitude of change in satiety scores from baseline ($r = 0.350$, $P = 0.023$). In the men, overconsumption after the preload containing sucrose ($r = -0.934$, $P = 0.020$) or milk ($r = -0.999$, $P < 0.001$) was a function of the magnitude of change in satiety scores from baseline; after the preload containing HFCS, this relation was not observed. Hunger ratings were significantly more suppressed at each time point after the milk preload than after the diet preload ($P < 0.05$). The change from baseline in GLP-1 concentrations was significantly larger ($P < 0.05$) 30 min after the milk preload (3.6 ± 3.4 pmol/L) than after the preloads containing sucrose (2.1 ± 2.3 pmol/L) or HFCS (2.1 ± 3.3 pmol/L). In men, this difference was observed at each time point ($P < 0.05$).

Furthermore, compensation and satiety ($r = 0.412$, $P < 0.05$) were positively related to change in pleasantness of taste after the preload containing sucrose (the greater the suppression in pleasantness of taste, the larger the satiety and compensation), as shown in **Figure 3**. Accordingly, plasma glucose concentrations were significantly higher over time after the drinks containing sucrose or HFCS than after the milk or diet preloads ($P < 0.001$). Moreover, plasma glucose concentrations were linearly related to the content of glucose of the preloads ($r = 0.581$, $P < 0.001$).

DISCUSSION

Do the satiation effects of isocaloric isovolumetric sucrose- or HFCS-containing preloads differ from those of milk as measured on the basis of VAS (in mm) or GLP-1 or ghrelin responses? The increase in satiety from baseline as AUC did not differ significantly between the sucrose, HFCS, or milk preload. Furthermore, satiety was expressed as compensation or overconsumption during the next meal; no significant differences between the different preloads were observed. From these observations we concluded that there are no differences in the satiety or energy balance effects of isovolumetric sucrose- or HFCS-containing preloads or milk.

Subsequently the mechanisms underscoring the increases in satiety were revealed. Although no differences in satiety were observed, the mechanisms underlying satiety due to sucrose- or HFCS-containing drinks or milk were different and were related to evoking different increases in satiety hormone concentrations.

No significant differences in energy intakes or in total energy consumed were observed 50 min after consumption of the 1.5-MJ (800 mL) drinks containing sucrose or HFCS. Also, energy intake after the isoenergetic isovolumetric milk preload did not differ from that after the sucrose or HFCS drinks. Similarly

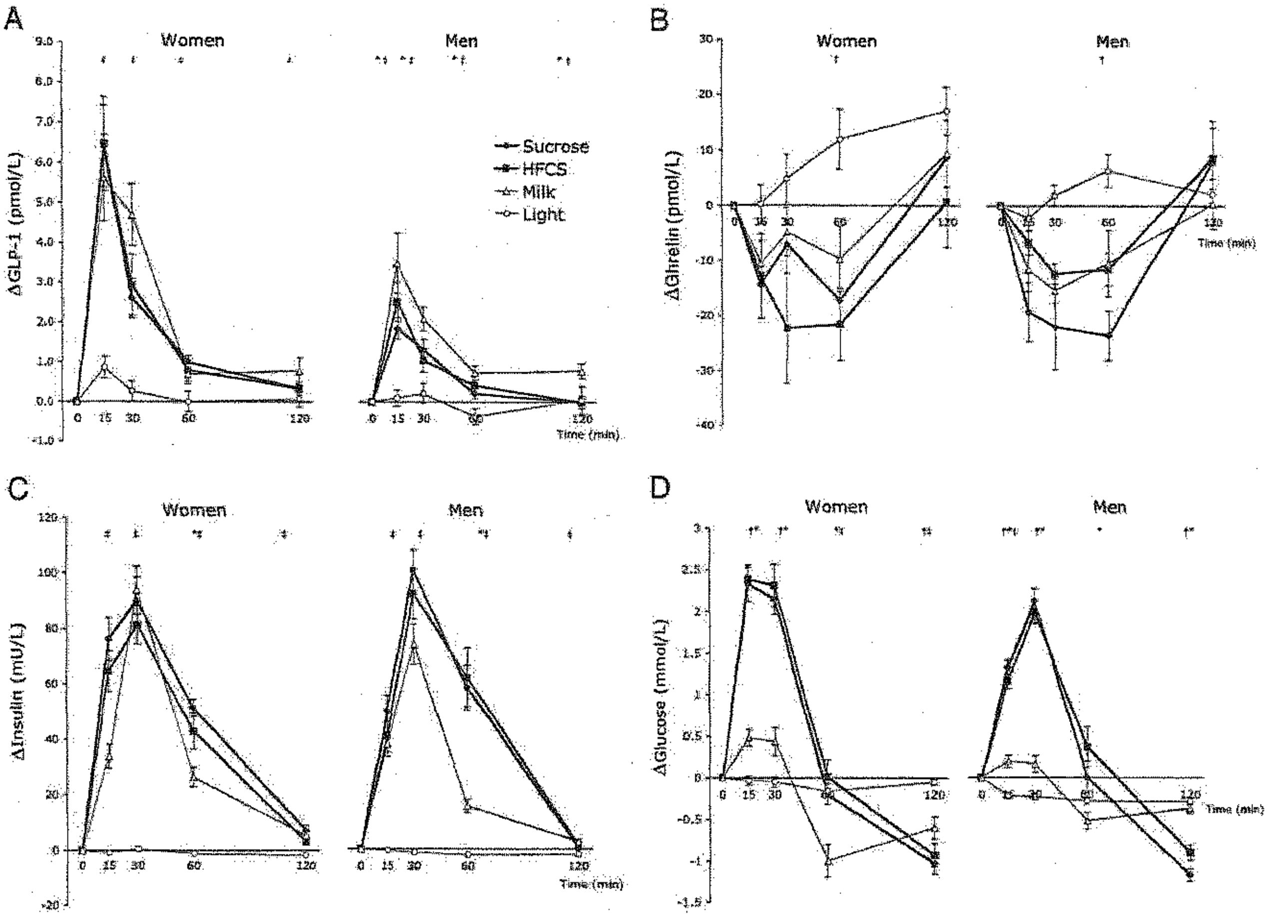

FIGURE 2. Mean (±SEM) change (Δ) in glucagon-like peptide 1 (GLP-1), ghrelin, insulin, and glucose of men ($n = 15$) and women ($n = 15$) as a function of preload condition. A: ‡Significant difference between the diet preload and the sucrose- and high-fructose corn syrup (HFCS)–containing preloads and the milk preload, $P < 0.005$ (ANOVA). *Significant difference between the milk preload and the sucrose- and HFCS-containing preloads, $P < 0.05$ (ANOVA); significant time-by-treatment interaction between the diet preload and the sucrose- and HFCS-containing preloads and the milk preload, $P < 0.001$ (repeated-measures ANOVA); significant time-by-sex interaction, $P < 0.01$ (repeated-measures ANOVA). B: †Significant difference between the diet preload and the sucrose- and HFCS-containing preloads, $P < 0.05$ (ANOVA); significant time-by-treatment interaction between the diet preload and the sucrose- and HFCS-containing preloads, $P < 0.05$ (repeated-measures ANOVA); the time-by-sex interaction was not significant (repeated-measures ANOVA). C: ‡Significant difference between the diet preload and the sucrose- and HFCS-containing preloads and the milk preload, $P < 0.001$ (ANOVA). *Significant difference between the milk preload and the sucrose- and HFCS-containing preloads, $P < 0.05$ (ANOVA); significant time-by-treatment interaction between the diet preload and the sucrose- and HFCS-containing preloads and the milk preload, $P < 0.001$ (repeated-measures ANOVA); the time-by-sex interaction was not significant (repeated-measures ANOVA). D: ‡Significant difference between the diet and the milk preloads, $P < 0.05$ (ANOVA). *Significant difference between the milk preload and the sucrose- and HFCS-containing preloads, $P < 0.001$ (ANOVA). †Significant difference between the diet preload and the sucrose- and HFCS-containing preloads, $P < 0.001$ (ANOVA); significant time-by-treatment interaction between the diet preload and the sucrose- and HFCS-containing preload, $P < 0.001$ (repeated-measures ANOVA); significant time-by-treatment interaction between the milk preload and the sucrose- and HFCS-containing preload, $P < 0.001$ (repeated-measures ANOVA); significant time-by-sex interaction, $P < 0.01$ (repeated-measures ANOVA).

to our observations, a previous study found no significant differences between the effects of cola or chocolate-milk consumption (0.9 MJ, 500 mL) with ad libitum intake 30 min later, despite significantly greater satiety 30 min after the chocolate milk (36) or in subsequent meal compensation 135 min after preloads (1.036 MJ, 590 mL) of cola, orange juice, and milk relative to sparkling water (37). As usual, energy intake including the energy-containing preloads was higher than total energy intake including the diet preload, despite the smaller consumption during the subsequent meal. Thus, subsequent energy intake only partly compensated for the energy delivered by the preloads; ie, for 45% with the sucrose-containing preload, for 42% with the HFCS-containing preload, and for 30% with the milk preload, all compared with energy intake after the diet preload. So, consumption of an energy-containing preload followed by a meal at 50 min led to overconsumption compared with a diet preload and subsequent meal. Previously, consumption of a 1.26-MJ high-fructose-glucose mixture (80–20%) was compensated with 12% of the meal consumed 60 min after preload, which was not different from that of an equisweet sucrose drink with 42% compensation (38). In conclusion, on the basis of these studies, subsequent energy intake did not differ significantly 30–135 min after a 0.9–1.5-MJ preload containing sucrose or HFCS or a milk preload. Therefore, in general, the effects of energy balance are positive, yet not different between different energy containing drinks.

A sex effect was observed in VAS ratings, energy intake, and energy compensation and overconsumption. A possible explanations for these sex differences was the different responses in GLP-1 and glucose when preloads of the same size were offered. Previous studies support these higher concentrations in women

TABLE 4
Satiety [change in area under the curve (ΔAUC)] as a function of the hormones glucagon-like peptide 1 (GLP-1) ghrelin, and insulin (ΔAUC) and correlations between GLP-1, ghrelin, and insulin (ΔAUC) and glucose (ΔAUC)[1]

	GLP-1		Ghrelin		Insulin	
Preload	*r*	*P*	*r*	*P*	*r*	*P*
All[2]						
Satiety	0.253	<0.01	—	—	0.241	<0.05
Sucrose[3]	0.382	<0.05	—	—	0.370	<0.05
HFCS[3]	0.429	<0.05	−0.407	<0.05	—	—
Milk[3]	—	—	0.423	<0.05	—	—
Diet[3]	—	—	—	—	—	—
All[2]						
GLP-1	—	—	—	—	—	—
Ghrelin	—	—	—	—	—	—
Insulin	0.36	<0.001	−0.19	<0.05	—	—
Glucose	—	—	−0.22	<0.05	0.49	<0.001

[1] HFCS, high-fructose corn syrup.
[2] n for all preloads was 120.
[3] n for each preload was 30.

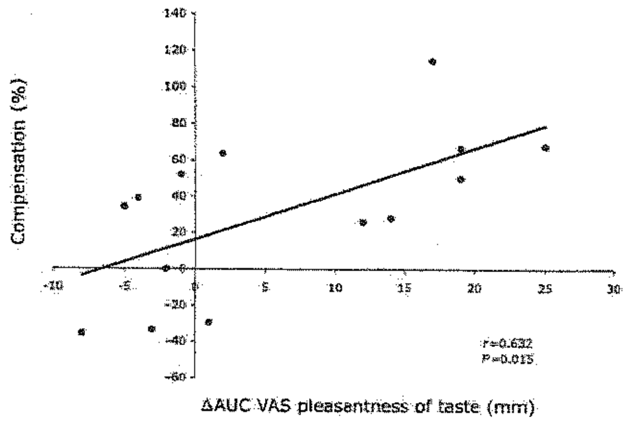

FIGURE 3. Compensation after the sucrose-containing preload in men and women (n = 14) as a function of the area under the curve (AUC; 0–50 min) of pleasantness of taste. Compensation = energy intake from diet − energy intake after any preload as a percentage of the preload. VAS, visual analogue scale.

(39, 40). Obviously, the preloads that were consumed by the men represented a smaller part of energy requirement than the preloads consumed by the women. Moreover, sex differences in water turnover may play a role (41) because it has been suggested that the increased energy intake after drinks may have been derived from physiologic mechanisms giving priority to quenching thirst (42). The preloads suppressed thirst equally, significantly more in women than in men however.

Are different mechanisms responsible for the satiety achieved after sucrose- or HFCS-containing preloads or a milk preload? Consumption of the preloads containing sucrose or HFCS caused similar changes in plasma concentrations of the hormones GLP-1, ghrelin, and insulin and of glucose. Also, leptin concentrations did not differ after consumption of either sucrose or HFCS (43). The increase in satiety was underscored by the increase in GLP-1 with the sucrose- or HFCS-containing preloads, but not with the milk preload. Because satiety did not differ between energy-containing preloads, it may well be that other satiety hormones such as peptide YY3-36 and cholecystokinin, which were not measured, supported the milk-induced satiety. Satiety after the sucrose-containing preload was also underscored by the increase in insulin and satiety after the HFCS-containing preload by the decrease in ghrelin. The changes in VAS ratings of the appetite profile were supported by the changes in the concentrations of the hormones GLP-1, ghrelin, and insulin and glucose. Stepwise regression showed that satiety was primarily related to increases in GLP-1 concentrations and secondarily to insulin concentrations. Thus, sucrose and HFCS likely trigger GLP-1 release, which may have triggered insulin release and a related increase in satiety.

TABLE 5
Energy intake from the meal and from the meal + preload, energy compensation, and energy overconsumption[1]

	Meal size[2]	Total energy intake (preload + meal)[3]	Compensation[4]	Overconsumption[5]
	kJ	*kJ*	%	%
Sucrose-containing preload				
Women	1742 ± 730[6]	3215 ± 730[6]	37 ± 37[6]	53 ± 53[6]
Men	2372 ± 794	3845 ± 794	53 ± 47	29 ± 30
HFCS-containing preload				
Women	1873 ± 868[6]	3347 ± 868[6]	28 ± 42[6]	57 ± 50[6]
Men	2335 ± 786	3808 ± 786	55 ± 54	29 ± 34
Milk preload				
Women	1945 ± 756[6]	3441 ± 756[6]	24 ± 42[6]	64 ± 60[6]
Men	2626 ± 880	4122 ± 880	36 ± 55	37 ± 34
Diet preload				
Women	2290 ± 773[6]	2292 ± 773[6]		
Men	3148 ± 984	3150 ± 984		

[1] All values are $\bar{x}$ ± SD; n = 40. HFCS, high-fructose corn syrup. The treatment-by-sex interaction was not significant (multivariate ANOVA).
[2,3] Significant difference between the diet preload and the other 3 preloads (ANOVA): [2] $P < 0.05$, [3] $P < 0.001$.
[4] Compensation = energy intake from the diet − energy intake after any preload as a percentage of the preload.
[5] Overconsumption = total energy intake from the diet − total energy intake after any preload as a percentage of the preload.
[6] Significantly different from men, $P < 0.05$ (ANOVA).

On the other hand, satiety and compensation after the preload containing sucrose correlated with change in pleasantness of taste. Individuals do not eat solely based on hunger, taste is another reason for eating a specific food, and a decrease in pleasantness of taste is often given as a reason for terminating or reducing food intake. Therefore, the less sweet, refreshing, and pleasant milk preload may have contributed to incomplete compensation at the subsequent meal. Furthermore, high glycemic carbohydrates have been shown to be associated with a reduced appetite and food intake in the very short term (eg, 1 h), whereas lower glycemic carbohydrates showed a more delayed effect on the perception of satiety (eg, 2–3 h) (44, 45). We found a linear relation between the glucose content of the preloads and AUC plasma glucose concentrations. The glycemic indexes (GIs) of the monosaccharides glucose, fructose, and lactose are 99, 19, and 46, respectively (46). The GI of sucrose is 68 (46) and of HFCS is 73 (47) and 68 (48). The glucose concentrations peaked at 30 min and dropped below baseline at 60 min after the carbohydrate preloads and remained low until the end of the experiment. The same pattern of an initial steep increase in plasma glucose and insulin concentrations followed by a rebound effect, which stimulates hunger and food intake, has been found in several studies (16, 17, 32, 49–56). Thus, a rapid rise in blood glucose and a large insulin response stimulates peripheral glucose uptake to such an extent that the blood glucose concentration falls below the fasting concentration. Therefore, the lower GI of milk, full-fat milk (GI: 27), and skim milk (GI: 32) (46), may have contributed to its satiety effect.

Is satiety after sucrose- or HFCS-containing preloads influenced by its biochemical properties? The carbohydrate sucrose is a disaccharide and consists of one molecule of glucose and one molecule of fructose, which are not available for absorption until sucrose is hydrolyzed by intestinal brush-border enzymes. HFCS, on the other hand, contains glucose and fructose in their monosaccharide forms, which gives the solution a higher osmotic pressure. In soft drinks, however, a proportion of the sucrose is hydrolyzed into glucose and fructose by the acidic pH before the drinks are consumed. Fructose is passively absorbed in the duodenum and jejunum by a GLUT 5 transporter, which has a smaller absorption capacity than does the actively sodium-dependent hexose transporter, which absorbs glucose in the duodenum (57–59). However, there is a more complete and faster transport accompanied by a decrease in malabsorption when fructose is consumed in combination with other carbohydrates (20, 21). Both the differences in duration in the intestines and in the osmotic pressure of glucose and fructose could influence satiety differently. Furthermore, glucose triggers glucose sensors in the central nervous system involved in the regulation of food intake (60). Fructose, however, does not cross the blood-brain barrier (61). Fructose could trigger satiety by its oxidation (62), greater thermogenic response (63–65), and rapid metabolism in the liver (61). The liver is sensitive to its own metabolism and signals to the brain via the vagus nerve to inhibit the central control for meal initiation (61). Thus, glucose and fructose in sucrose- or HFCS-sweetened drinks contribute to satiety through different biochemical mechanisms.

In summary, a 1.5-MJ preload containing sucrose or HFCS or a milk preload did not affect energy intake differently 50 min later. Differences in satiety were absent despite different mechanisms underlying satiety due to sucrose- or HFCS-containing drinks or milk. Sucrose and HFCS triggered GLP-1 release, which triggered insulin release and a related increase in satiety. The different responses in GLP-1, glucose, and thirst when preloads of the same sizes were offered could explain the sex effect that was observed in VAS ratings, energy intake, and energy compensation and overconsumption. Obviously, the preloads that were consumed represented a smaller part of the energy requirement in men than in women.

On the basis of partial compensation for and overconsumption due to the energy-containing preloads, a long-term study to assess the effect on body weight regulation would be a necessary follow-up. The question remains whether, in the long-term, this partial overconsumption of $\approx$40–50% of the meal, amounting to 1 MJ, will accumulate. If no other long-term compensating mechanisms occurred, an increase in body weight over time of $\approx$1 kg over 1 mo would occur. Here, an additional 30 MJ accounts for a gain in body weight of 1 kg (66). To confirm this hypothetical approach or to find long-term compensating mechanisms, a well-controlled long-term study would be necessary.

In conclusion, despite differences in the biochemical properties of preloads containing sucrose, HFCS, or milk and differences in the mechanisms underlying satiety in relation to GLP-1 release and ghrelin release, no differences in satiety, compensation, or overconsumption were observed.

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SS designed the experiment, collected the data, analyzed the data, and wrote the manuscript. MSW-P designed the experiment, helped analyze the data and write the manuscript, and supervised the project. None of the authors had any financial or personal interest in any company or organization sponsoring the research.

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High Fructose Corn Syrup and Sugar

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Sugars and satiety: does the type of sweetener make a difference?[1–3]

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ABSTRACT

Background: Widespread use of high-fructose corn syrup (HFCS) in beverages has been linked to rising obesity rates. One hypothesis is that HFCS in beverages has little satiating power.

Objective: The objective of the study was to compare the relative effect of commercial beverages containing sucrose or HFCS on hunger, satiety, and energy intakes at the next meal with the use of a within-subject design.

Design: Thirty-seven volunteers (19 men, 18 women) aged 20–29 y consumed isocaloric cola beverages (215 kcal) sweetened with sucrose, HFCS 42, or HFCS 55. HFCS 42 contains 42% fructose, and HFCS 55 contains 55% fructose. Diet cola (2 kcal), 1%-fat milk (215 kcal), and no beverage were the control conditions. The 5 beverages were consumed at 1010 (2 h after a standard breakfast). Participants rated hunger, thirst, and satiety at baseline and at 20-min intervals after ingestion. A tray lunch (1708 kcal) was served at 1230, and energy intakes were measured. The free sugars content of sucrose-sweetened cola was assayed at the time of the study.

Results: We found no differences between sucrose- and HFCS-sweetened colas in perceived sweetness, hunger and satiety profiles, or energy intakes at lunch. The 4 caloric beverages tended to partially suppress energy intakes at lunch, whereas the no-beverage and diet beverage conditions did not; the effect was significant ($P < 0.05$) only for 1%-fat milk. Energy intakes in the diet cola and the no-beverage conditions did not differ significantly.

Conclusion: There was no evidence that commercial cola beverages sweetened with either sucrose or HFCS have significantly different effects on hunger, satiety, or short-term energy intakes. *Am J Clin Nutr* 2007;86:116–23.

KEY WORDS Beverages, sucrose, fructose, high-fructose corn syrup, HFCS, sweetness, hunger, fullness, satiety, energy intakes

INTRODUCTION

The introduction of corn sweeteners into the US food supply is said to have contributed to the current obesity epidemic (1–3). High-fructose corn syrup (HFCS) began to replace sucrose in soft drinks at approximately the same time that obesity rates in the United States began their sharp increase (2, 4). However, temporal parallels between HFCS consumption patterns and body-weight trends are not sufficient to show causality. Obesity has also increased sharply in countries where beverage consumption is lower than in the United States and HFCS is not a common sweetener (5).

One of the criteria for establishing causality in evidence-based medicine is a biologically plausible mechanism. Attempts to establish a causal link between soft drink consumption and rising obesity rates have therefore relied on the notion that caloric beverages in general (6), and HFCS-sweetened beverages in particular (2, 7), lack satiating power. Research reports have suggested that liquids were less satiating than were solids (8); that sugars were less satiating than was either protein or fat (9); and that HFCS blunted the satiety response more than did other sweeteners (2, 10, 11). The metabolic and endocrinologic processes associated with the ingestion of free fructose have featured prominently in arguments that HFCS-sweetened beverages are the principal culprit in the obesity epidemic (2, 6, 7).

However, satiety-related arguments based on the ingestion of pure fructose or fructose-rich stimuli (12, 13) may not apply to sweetened beverages, given that the 2 most common forms of HFCS—HFCS 55 and HFCS 42—contain 55% and 42% free fructose, respectively, and the remainder is free glucose. Furthermore, the sharp distinctions made between HFCS-sweetened and sucrose-sweetened beverages (2, 14) may be incorrect. The low pH of carbonated soft drinks favors the breakdown of sucrose into free glucose and free fructose before consumption (15), and the rate of hydrolysis is dependent on storage variables, temperature, and time (16). Perhaps most important, the short-term satiating power of foods and beverages may have little to do with the long-term regulation of body weight (13, 17).

The present study was a direct test of the hypothesis that HFCS-sweetened carbonated soft drinks differ significantly from sucrose-sweetened soft drinks and from low-fat milk in their effect on satiety. Aiming to approximate naturalistic conditions of soft drink use, we compared the effect of commercially available cola beverages, sweetened with sucrose or with 2 types of HFCS (HFCS 42 and HFCS 55), on hunger, satiety, and energy intakes (EIs) at the test meal. Because so much has been made of the metabolic differences between free fructose and fructose bound within disaccharide sucrose molecules (2, 14), we sent samples of the sucrose-sweetened beverage to be analyzed for free sugars content at the time of the experiment.

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SUBJECTS AND METHODS

Participants

Thirty-seven participants (19 M, 18 F) aged 20–29 y were recruited at the University of Washington with the use of advertisements and flyers. A telephone-administered screening interview was used to verify eligibility criteria. Eligible participants were normal-weight to overweight [body mass index (BMI; in kg/m^2): 18–30], regularly consumed breakfast, did not smoke, and were not following a diet to gain or lose weight. Persons with food allergies or food restrictions; those who disliked ≥2 of the foods or beverages in the study; those taking prescription medications that were likely to affect taste, smell, or appetite; athletes in training; pregnant or lactating women; and persons reporting recent weight loss or weight cycling were excluded. Potential candidates were invited to report to the laboratory for a brief session, during which their weight and height were measured. The Eating Disorder Inventory (18) and the cognitive restraint subscale of the Eating Inventory (19) were administered as screening instruments to exclude persons with indications of eating disorders or restrained eating patterns. Persons who met all eligibility criteria were invited to participate and were given a reminder card stating the dates and times for the study sessions. To minimize variability, each participant was asked to report to the laboratory on the same day of the week throughout the study, to keep evening meals and activity levels on the day before each test as similar as possible, to refrain from drinking alcohol the day before each test, and to have a standardized breakfast at ≈0800 on the mornings when they were scheduled to have a test. The participants' standardized breakfasts were consumed at home and were composed of specified servings of hot or cold cereals with milk along with a medium-sized apple, orange, or banana or a specified serving of low-fat yogurt along with a medium-sized fruit.

All participants provided written informed consent. The study protocol was approved by the Institutional Review Board at the University of Washington. All 37 subjects completed the study and were compensated for their time.

Study design

The study followed a repeated-measures within-subject design, in which each participant returned for 6 separate test sessions. The sessions lasted from 0930 to 1310 and were spaced at least a week apart. The order of presentation of the 5 preloads and the no-beverage condition was counterbalanced. The same lunch foods were offered on all 6 testing occasions. The magnitude of the energy manipulation (0 or 215 kcal) was based on a review of previous studies in this area (20). Power analysis indicated that, with a power of 80% and an alpha of 0.05, a sample of 35 subjects was sufficient to detect a minimum difference of 150 kcal in compensation (21).

Beverage stimuli

The 5 beverages were cola sweetened with HFCS 42 (Sam's Choice Cola; Cott Beverages, Toronto, Canada), cola sweetened with HFCS 55 (Coca-Cola Classic; Coca-Cola Co, Atlanta, GA), cola sweetened with sucrose (Coca-Cola Classic), cola sweetened with aspartame (Diet Coke; Coca-Cola Co), and 1%-fat milk (Darigold; Wesfarm Foods, Seattle, WA). All preload beverages with the exception of the diet cola (2 kcal) were isoenergetic (894 kJ or 215 kcal) and of comparable sweetness, but they differed in sugar composition. To keep both sweetness and energy constant, the preload volume was allowed to vary within narrow limits (from 475 to 525 mL). The composition and energy density of the 5 beverage preloads are shown in **Table 1**. All beverages were coded and were served chilled, without ice, in opaque containers with a lid and a straw. Participants were asked to consume the entire amount within 15 min.

TABLE 1
Energy and macronutrient composition of the preloads[1]

Preload	Sugar composition (fructose/glucose)	Sugars	Protein	Fat	Serving	Energy	Energy density
	%/%	*g*	*g*	*g*	*mL*	*kcal*	*kcal/g*
HFCS 42	42/58	57.3	0.0	0.0	475	214	0.45
HFCS 55	55/45	57.7	0.0	0.0	525	213	0.44
Sucrose	50/50	54.7	0.0	0.0	525	213	0.44
Aspartame	0/0	0.0	0.0	0.0	475	2	0.00
1%-fat Milk	0/50[2]	27.2	16.7	5.2	495	213	0.43

[1] HFCS 42 and HFCS 55, High-fructose corn syrup–sweetened cola containing 42% and 55% fructose, respectively; sucrose, sucrose-sweetened cola; aspartame, aspartame-sweetened cola. Data were from ESHA software (FOOD PROCESSOR version 8.1; Salem, OR) and manufacturers' specifications.

[2] Lactose in milk is a disaccharide made up of 1:1 glucose:galactose.

Samples of the sucrose-sweetened beverage were analyzed at regular intervals during the data collection phase. The analyses, conducted by the Analytic Chemistry Department of the Coca-Cola Company, used samples from the same production run (25 May 2005) of Coca-Cola Classic and were conducted at the same time as the data collection phase of the present study.

Motivational ratings and hedonic evaluations

Participants used computerized, semi-anchored visual analogue scales (VASs) to rate their hunger, fullness, thirst, nausea, and desire to eat. The VAS software was custom-written by using the LABVIEW graphic programming software (version 6.1; National Instruments, Austin, TX) that was running on 10 identical Macintosh G3 computers (Apple Computers, Cupertino, CA). Motivational scales were presented one at a time (ie, one scale per screen) on the computer monitor. Each participant used a mouse to position a cursor along the 100-mm bar displayed on a flat-panel LCD computer monitor. The VAS bars were anchored at each extreme with the labels "not at all . . ." and "extremely . . ." (22). A semi-anchored VAS was also used for quantifying several sensory and hedonic attributes of each beverage. Each sensory attribute scale also was anchored with the labels "not at all..." and "extremely . . .". Hedonic ratings and ratings along 11 sensory attribute scales were obtained for each beverage.

Test meal

A lunch meal served on a tray was provided at 1230. Identical meals were provided on each occasion. The set meal was 7120 kJ (1708 kcal) and included a variety of foods, both savory and sweet. Each lunch consisted of a selection of 2 grains, 2 types of fruit, 2 vegetables, 2 cheeses, 2 meats, 2 candies, 1 yogurt, 1 ice cream cup, hummus, chips, and water. A large cup containing 591 mL (20 fl oz) still water was provided with the test lunch. Participants were told that they could have as much or as little as

TABLE 2
Energy and nutrient composition of foods provided at lunch[1]

Food	Carbohydrate	Protein	Fat	Sugar	Fiber	Portion	Energy
	g	*g*	*g*	*g*	*g*		*kcal*
Reduced-fat crackers	21	3	3		3	7 pieces	120
Pita bread	36	7	2	1	3	1 piece	190
Banana, medium-sized	26.7	1.2	0.6		1.8	1 piece	105
Apple slices	8	0	0	6	0	1 bowl	35
Baby carrots	9	1	0	6	2	1 bowl	38
Sugar snap peas	7	2	0	3	2	1 bowl	40
Cheddar cheese	0	5	7	0	0	1 slice	90
Havarti cheese	0	6	10	0	0	1 slice	110
Yogurt (99% fat-free)	33	5	1.5	27	0	1 pack	170
Ham	2	10	1	2	0	2 slice	60
Turkey	0	20	1	0	0	2 slice	90
Hummus	24	8	16	0	0	8 tbsp	240
Chocolate candies	15	1	4.5	13	1	1 pack	100
Marshmallow snack bar	18	1	2	8	0	1 pack	90
Potato chips	12	1	10	0	0	1 pack	140
Vanilla ice cream and orange sherbet blend	15	1	3	13	0	1 pack	90
Totals	226.7	72.2	61.6	79	12.8	—	1708

[1] Information was obtained from the food label or ESHA software (FOOD PROCESSOR version 8.1; Salem, OR).

they would like of any food or water and that they could request unlimited additional portions. All foods and water were weighed at the time of serving. Plate waste was collected and weighed by the experimenters. Food energy and nutrient values were calculated with FOOD PROCESSOR software (version 8.1; ESHA Research, Salem, OR) and from the manufacturer's food labels. The nutrient composition of the meal is shown in **Table 2**.

Procedures

Participants were asked to consume a standard breakfast at home starting at 0800. They arrived at the laboratory at 0930 and were seated in separate cubicles. They remained there for the duration of the session and were allowed to read, listen to music with earphones, or use their portable computers. They were allowed to leave the room briefly to stretch or use the restroom. Participants were also asked to record all foods and beverages they had consumed for breakfast earlier that morning and to note the time of consumption. Motivational ratings were first obtained 10 min after arrival (baseline or time 0) and every 20 min thereafter until lunchtime (times 1 through 8). The preload was provided in the laboratory at 1010, and lunch was provided at 1230. The last set of ratings was obtained after lunch (time 9), after which participants left the laboratory.

Data analyses and statistical tests

We used SPSS for WINDOWS software [version 11.1 (23)] for all analyses. Normality was determined by the Kolmogorov-Smirnov test (normal if $P > 0.05$). Analyses of motivational ratings used a nested repeated-measures analysis of variance (ANOVA) with beverage type and time after ingestion (times 2–8) as the within-subjects factors and sex as the between-subjects factor. Analyses were conducted for all 6 conditions together and separately for the 3 sweetener conditions (sucrose, 42% HFCS, and 55% HFCS) and the 3 comparison conditions (aspartame, 1%-fat milk, and no beverage). Univariate tests of within-subject effects were subject to Huynh-Feldt correction when the sphericity assumption was violated. Bonferroni-adjusted pairwise comparisons were made when ANOVAs were significant. Because there were no significant main effects or sex-related interactions ($P > 0.05$ for all tests), the data were combined by sex for each beverage condition. Analyses of EIs and the weight of foods and water consumed at lunch used a repeated-measures ANOVA with beverage type as the within-subject factor and sex as the between-subjects factor. The strength of the association between prelunch (time 8) appetite ratings and energy or water intakes at lunch was tested by using Pearson's correlation coefficients. Prelunch appetite ratings were computed by averaging 3 proxies for appetite according to a method similar to that of Anderson et al (11): hunger, desire to eat, and the inverse of fullness (ie, 100 − fullness). Sweetness intensity and hedonic ratings were analyzed by repeated-measures ANOVA.

RESULTS

Participants and beverage stimuli

Mean (±SD) age was 22.6 ± 4.0 y for men and 23.4 ± 2.8 y for women. Mean body weight was 77.5 ± 10.7 kg for men and 60.2 ± 9.1 kg for women. Body mass index (BMI; in kg/m^2) values were 23.4 ± 1.8 for men and 21.9 ± 2.7 for women.

Analysis of sweetness ratings for the 4 cola beverages found a significant ($F_{3, 99} = 11.1$, $P < 0.001$) main effect of beverage type. However, that was entirely due to the aspartame-sweetened cola, which was perceived as significantly less sweet than the 3 sugar-sweetened colas ($P < 0.01$ for all 3 comparisons). Cola beverages sweetened with sucrose, HFCS 55, and HFCS 42 did not differ significantly in perceived sweetness ratings. Milk (1% fat) was not perceived as sweet. All 5 beverages (including milk) were rated as equally palatable by the participants. The analysis of hedonic preference ratings showed no significant main beverage effect ($F_{41, 32} = 2.5$).

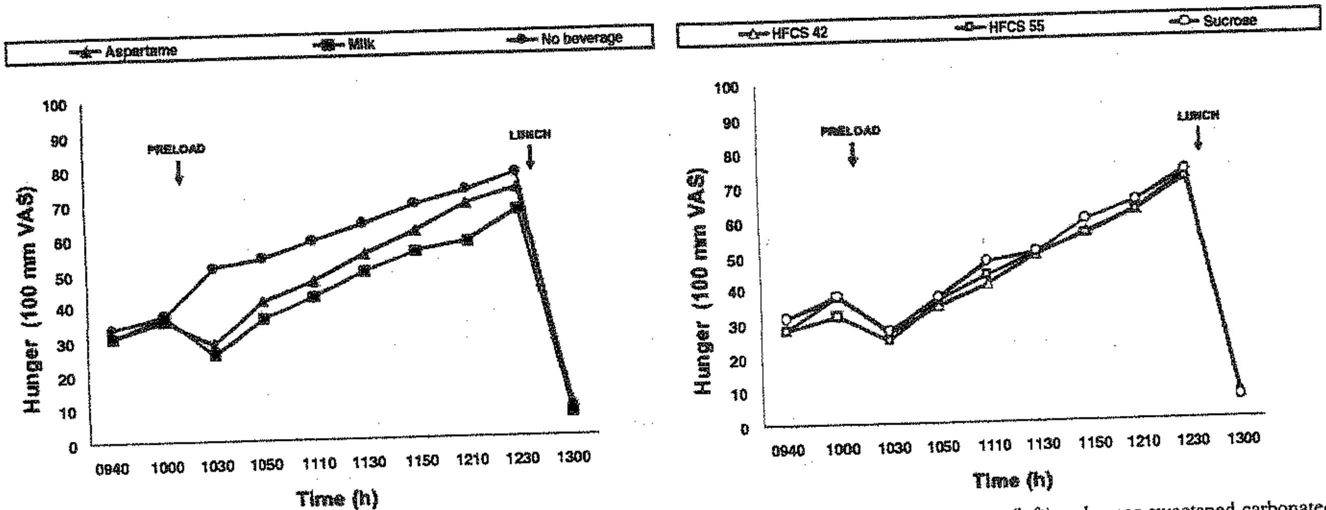

FIGURE 1. Temporal profiles of mean hunger ratings as a function of preload condition for control beverages (left) and sugar-sweetened carbonated beverages (right). $n = 37$. VAS, visual analogue scale; HFCS 42 and 55, high-fructose corn syrup containing 42% and 55% fructose, respectively. The no-beverage control was associated with higher hunger levels than were the milk and aspartame-sweetened diet cola controls ($P < 0.005$), and the beverage × time interaction was significant ($P < 0.005$). Hunger ratings for the 3 sugar-sweetened beverages did not differ significantly.

Motivational ratings

All 5 beverages (caloric and not) led to lower hunger ratings during the initial 20 min after ingestion than were seen in the no-beverage condition. Repeated-measures ANOVA showed significant main effects of both beverage type and time and a significant beverage × time interaction ($P < 0.001$ for all). Separate analyses were then conducted for the 3 colas and the 3 comparison conditions.

The time course of energy and volume effects on short-term hunger is shown in **Figure 1** (left). In the first 60 min after their ingestion, equal volumes of 1%-fat milk and noncaloric diet cola had comparable effects on perceived hunger. However, hunger ratings rose more rapidly in the diet cola condition than in the milk condition, and a separation in hunger ratings was visible before lunch. ANOVA found a significant ($P < 0.001$) main effect of beverage type and a significant ($P < 0.005$) beverage × time interaction.

In contrast, the 3 sugar-sweetened cola beverages, although different from the no-beverage condition, did not differ significantly from each other (Figure 1, right). There was no significant main beverage effect or beverage × time interaction.

ANOVA of fullness ratings found significant main effects of beverage type and time ($P < 0.001$ for both) and a significant beverage × time interaction ($P < 0.005$). As shown in **Figure 2** (left), milk and diet cola had different effects on fullness ratings, depending on the time after ingestion. The beverage effect and the beverage × time interaction were significant ($P < 0.01$ for both). In contrast, the sucrose- and the HFCS-sweetened colas differed significantly ($P < 0.001$) from the no-beverage condition but not from each other. The beverage × time interaction was not significant (Figure 2, right).

Analysis of the desire-to-eat ratings found significant main effects of beverage type and time ($P < 0.001$ for both) and a significant beverage × time interaction ($P < 0.01$). It can be seen

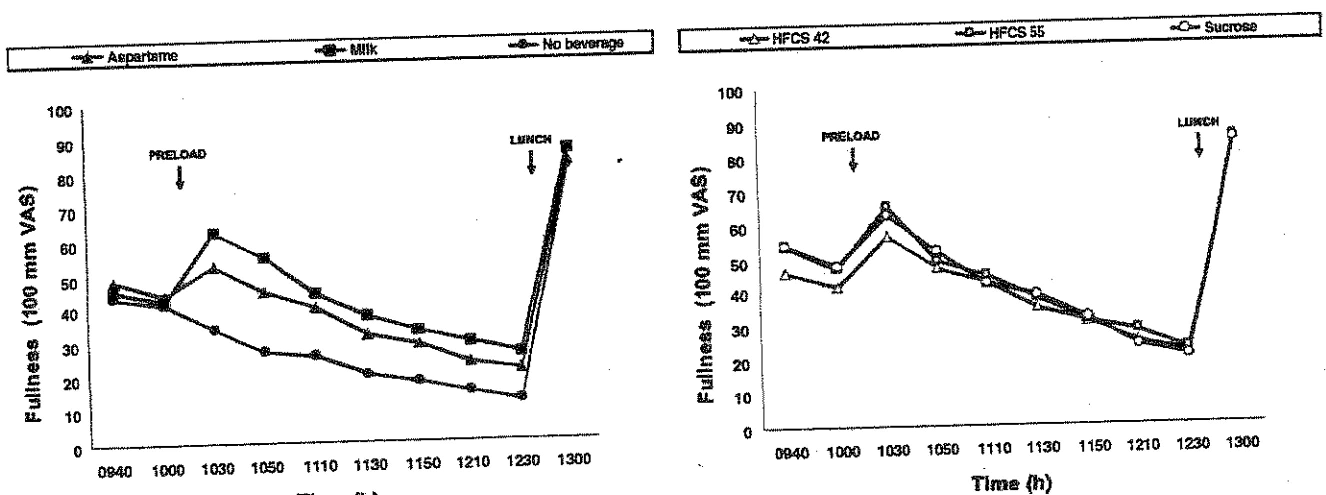

FIGURE 2. Temporal profiles of mean fullness ratings as a function of preload condition for control beverages (left) and sugar-sweetened carbonated beverages (right). $n = 37$. VAS, visual analogue scale; HFCS 42 and 55, high-fructose corn syrup containing 42% and 55% fructose, respectively. The no-beverage control was associated with significantly lower fullness ratings than were the milk and aspartame-sweetened diet cola controls ($P < 0.001$ for both). Diet cola was associated with significantly lower fullness ratings than was milk ($P < 0.05$), and the beverage × time interaction was significant ($P < 0.01$). Fullness ratings for the 3 sugar-sweetened beverages did not differ significantly.

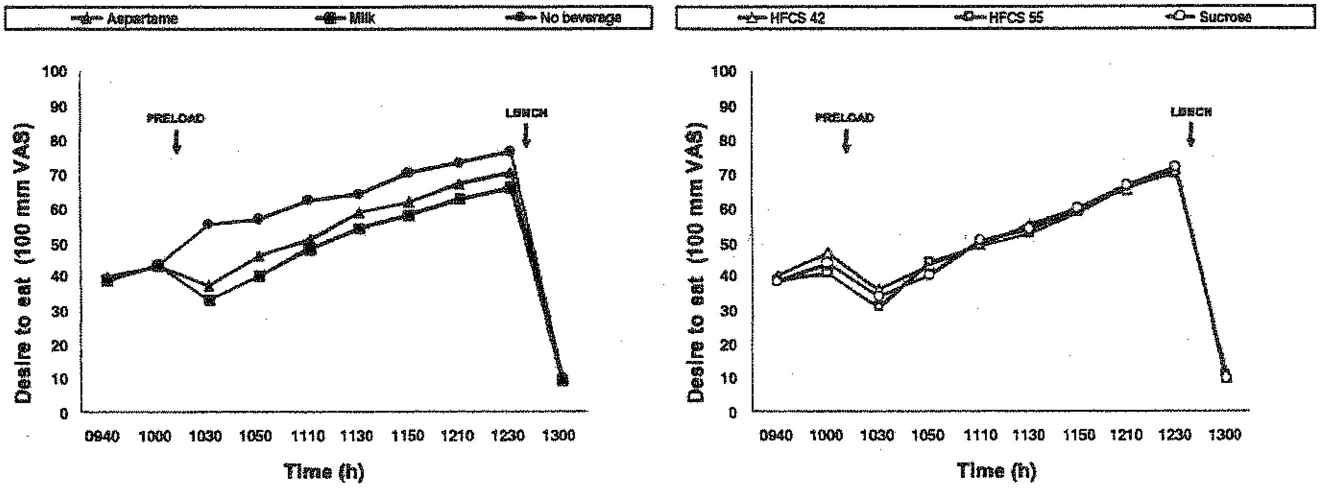

FIGURE 3. Temporal profiles of the mean desire to eat as a function of preload condition for control beverages (left) and sugar-sweetened carbonated beverages (right). n = 37. VAS, visual analogue scale; HFCS 42 and 55, high-fructose corn syrup containing 42% and 55% fructose, respectively. The no-beverage control was associated with a significantly greater desire to eat than were the milk and aspartame-sweetened diet cola controls ($P < 0.005$), and the beverage × time interaction was significant ($P < 0.05$). Desire-to-eat ratings for the 3 sugar-sweetened beverages did not differ significantly.

in **Figure 3** (left) that 1%-fat milk and diet cola had different effects on the desire to eat, depending on the time after ingestion. The effect of beverage type was significant ($P < 0.001$), as was the beverage × time interaction ($P < 0.05$). Again, the sucrose- and the HFCS-sweetened colas did not differ significantly from each other (Figure 3, right).

Analysis of thirst ratings (**Figure 4**) found significant main effects of beverage type and time ($P < 0.001$ for both). The beverage × time interaction also was significant ($P < 0.01$). Subjects in the no-beverage condition reported significantly higher thirst ratings than did those in the other 5 conditions ($P < 0.05$ for all comparisons). The 5 beverages did not differ significantly from each other in thirst ratings. Participant nausea ratings did not vary significantly by preload condition, and nausea did not vary significantly as a function of time.

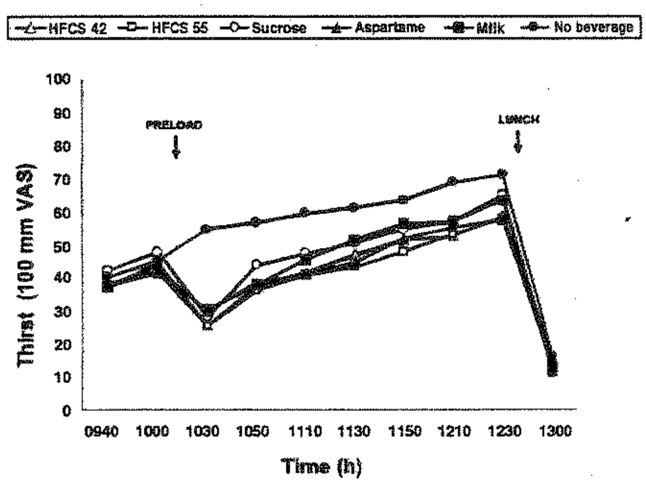

FIGURE 4. Temporal profiles of mean thirst ratings as a function of preload condition for all 6 preload conditions. n = 37. VAS, visual analogue scale; HFCS 42 and 55, high-fructose corn syrup containing 42% and 55% fructose, respectively. The no-beverage control was associated with significantly greater thirst than were the milk and aspartame-sweetened diet cola controls ($P < 0.001$), and the beverage × time interaction was significant ($P < 0.05$). Thirst ratings for the 3 sugar-sweetened beverages did not differ significantly.

Energy and nutrient intakes

For each condition, energy and water intakes at lunch, as well as the weight of all foods consumed, are shown in **Table 3**. Across all 6 conditions, men consumed an average of 1077 kcal at lunch, whereas women consumed an average of 862 kcal. Whereas this effect of sex on EIs was significant ($P < 0.005$), the beverage type × sex interaction was not.

The 4 caloric beverages partially suppressed EIs at lunch as compared with the EIs in the no-beverage condition. The main effect of beverage type on EIs was significant ($P < 0.05$). However, pairwise comparisons showed that the effect was significant only for the 1%-fat milk preload ($P < 0.05$). EIs in the no-beverage condition and in the diet cola condition did not differ significantly, which indicated that preload volume had no effect on EIs by the time the test lunch was served (120 min after preload ingestion).

The combined energy content of the preload and the lunch also showed significant main effects of beverage type ($P < 0.001$). Pairwise comparisons showed that the 3 sugar conditions did not differ significantly from each other or from milk. However, all 4 caloric beverages differed significantly from both the diet cola and the no-beverage conditions.

Beverage type significantly affected the weight of food and the amount of water consumed at lunch ($P < 0.001$ for both). Participants in the no-beverage condition consumed significantly more water at lunch than did subjects in all of the other preload conditions except for the diet cola condition. The nutrients consumed in association with each beverage condition are shown in **Table 4**. Beverage type did not significantly affect the nutrient composition of the lunch meal. Overall, the meals selected and consumed by the participants provided 51.2% of energy as carbohydrate, 17.2% of energy as protein, and 32.8% of energy as fat. The nutrient composition of lunch did not differ significantly by sex.

Motivational ratings and energy intakes

A composite score of appetite was calculated by using the method of Anderson et al (11). The correlation between appetite ratings and EIs at lunch was significant for women (r = 0.33,

TABLE 3
Energy and water intakes and the weight of foods and beverages consumed at lunch for each preload condition[1]

Preload condition	Energy at lunch	Energy at lunch + preload	Volume of water at lunch	Weight of food at lunch without water
	kcal	*kcal*	*mL*	*g*
HFCS 42	979 ± 40	1193 ± 40[2]	415 ± 29	1004 ± 44[2]
HFCS 55	969 ± 41	1182 ± 41[2]	418 ± 27	1003 ± 39[2]
Sucrose	957 ± 41	1170 ± 41[2]	427 ± 31	1009 ± 44[2]
Aspartame	1009 ± 39	1011 ± 39	437 ± 28	1033 ± 40
1%-fat Milk	916 ± 41[2]	1129 ± 41[2]	423 ± 26	961 ± 42[2]
No beverage	1008 ± 40	1008 ± 41	522 ± 36‡	1125 ± 44

[1] All values are $\bar{x}$ ± SEM; $n = 37$. HFCS 42 and HFCS 55, high-fructose corn syrup–sweetened colas containing 42% and 55% fructose, respectively; sucrose, sucrose-sweetened cola; aspartame, aspartame-sweetened cola.
[2] Significantly different from aspartame and no-beverage conditions, $P < 0.05$ (Bonferroni-corrected post hoc pairwise comparison).
[3] Significantly different from all beverage conditions except aspartame, $P < 0.05$ (Bonferroni-corrected post hoc pairwise comparison).

$P < 0.001$) but not for men ($r = 0.17$, NS). In contrast, the correlation between prelunch thirst ratings and water consumption at lunch was significant for both women ($r = 0.39$, $P < 0.001$) and men ($r = 0.2$, $P < 0.05$).

Free sugar content of sucrose-sweetened beverage

The progressive hydrolysis of sucrose in cola beverages over the course of the study is shown in **Figure 5**. Each point is based on the analysis of 3 samples. As sucrose hydrolyzed, its concentration declined from 36% of total sugars on June 30 to just above 10% on August 24, or ≈3 mo after the beverages were manufactured (May 25). Free fructose increased from 32% to ≈44%. Free glucose (not shown) followed the same course as fructose. During the time of the satiety study (period indicated by the shaded bar), the principal sugars in the sucrose-sweetened cola were free fructose and glucose. Dashed reference lines at 50.6% and 6.4% indicate concentrations of sucrose present in samples from a separate lot of sucrose-sweetened cola measured 10 d and 1 y after manufacture.

DISCUSSION

The argument that HFCS-sweetened beverages play a causal role in the obesity epidemic (24) rests, in part, on the notion that free fructose blunts the satiety response more strongly than do other sweeteners (2, 11, 13). Bray et al (14) made a sharp distinction between "free" and bound fructose in soft drinks, arguing further that HFCS-containing beverages could "never" have the same sweetness as sucrose-sweetened ones.

TABLE 4
Macronutrient intakes at lunch[1]

Preload condition	Protein	Carbohydrate	Sugar	Fat
	kcal	*kcal*	*kcal*	*kcal*
HFCS 42	165 ± 8	507 ± 21	181 ± 11	319 ± 17
HFCS 55	169 ± 9	503 ± 23	179 ± 10	310 ± 16
Sucrose	171 ± 9	482 ± 23	173 ± 12	315 ± 15
Aspartame	181 ± 9	504 ± 21	183 ± 10	338 ± 16
1%-fat Milk	156 ± 10	466 ± 22	161 ± 12	307 ± 15
No Beverage	166 ± 10	524 ± 21	195 ± 12	334 ± 15

[1] All values are $\bar{x}$ ± SEM; $n = 37$. HFCS 42 and HFCS 55, high-fructose corn syrup–sweetened colas containing 42% and 55% fructose, respectively; sucrose, sucrose-sweetened cola; aspartame, aspartame-sweetened cola.

As the present study shows, the 3 cola beverages, which were sweetened with sucrose, HFCS 55, or HFCS 42, were perceived as equally sweet and significantly sweeter than diet cola. All 3 beverages showed identical temporal profiles of motivational ratings, which were different from the no-beverage condition. There were no differences between the reported temporal profiles for hunger, satiety, and the desire to eat obtained after the ingestion of HFCS- or sucrose-sweetened colas. Compared with the EIs under the no-beverage condition, the 3 colas and 1%-fat milk weakly suppressed EIs at lunch, whereas the diet cola did not. However, the effect was significant only for 1%-fat milk.

The present study used the conventional preload paradigm (25–27) and commercially available colas and 1%-fat milk. The statistical power was similar to that used in past research (9, 25). The study design was thus able to separate the effects of preload energy and preload volume. As had been noted in previous reports, diet cola suppressed hunger immediately after ingestion, but hunger ratings recovered sooner than did those after ingestion of caloric 1%-fat milk. Preload volume alone had no effect on EIs 120 min later. The amount of food consumed at lunch in the diet

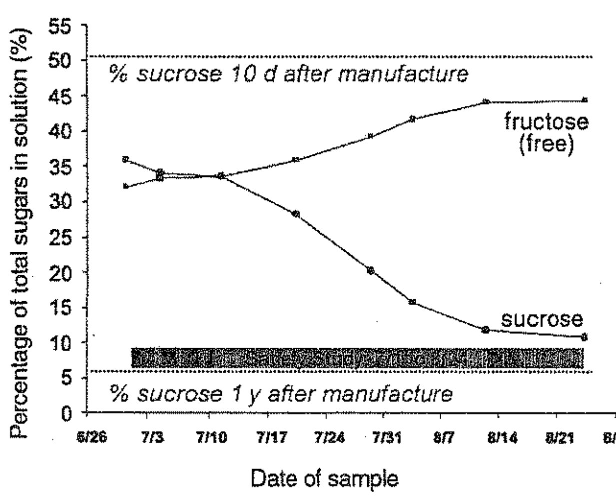

FIGURE 5. Timeline of sucrose inversion in the sucrose-containing cola used in this study. Each data point represents the mean of 3 samples taken from the same lot on the indicated date. As sucrose hydrolyzed over the weeks of the study, its concentration declined from 36% of total sugars to just above 10%. Free fructose increased from 32% to ≈45% of total sugar.

cola condition did not differ significantly from that in the no-beverage condition.

The notion that HFCS-sweetened beverages differ substantially from sucrose-sweetened beverages (2, 14) seems to have been based on the incorrect assumption that sucrose in solution remains stable. As documented by multiple laboratory assays conducted over the course of the present study, the sucrose content of the cola beverage dropped from 35% to 10%, whereas the free fructose content rose from 32% to 44% of total sugars. Other hydrolysis data indicate that 50% of the sucrose in carbonated beverages is hydrolyzed within 10 d of manufacture and that ≈90% is hydrolyzed within 3 mo. Given the time lag between production and consumption, it is likely that most sugars in sucrose-sweetened beverages are already in the form of free fructose and glucose by the time the beverages are consumed (16).

Previous laboratory studies of sugars and satiety in humans, most often conducted with aqueous solutions of pure sugars (11, 12), produced inconsistent results. One early study did not find differences between glucose and fructose in hunger ratings or EIs (12). A study in 16 women showed that 50 g fructose in 500 mL water significantly reduced lunch intakes as compared with a water control (28). A study of different glucose-fructose mixtures showed that high-glucose (80%) stimuli elevated blood glucose concentrations more than did high-fructose stimuli (80%), but that the 2 mixtures had similar effects on appetite (T Akhavan and GH Anderson, unpublished observations, 2005). The same study showed that high-fructose stimuli (65% and 80%) were associated with lower short-term food intake than was sucrose.

The putative effect of HFCS on satiety hormones awaits further research. In a recent study, 30 lean women consumed cola beverages at lunch served at 1300 h, and blood samples were drawn before the meal and 30 min and 60 min afterward (29). There were no significant differences between plasma glucose, insulin, leptin, or ghrelin after the ingestion of HFCS- or sucrose-sweetened cola. It is possible that the responses to sucrose- and HFCS-sweetened cola beverages were similar because the sugar content of the stimuli was, in fact, much the same. Studies of the human response to sweetened liquids should assess the stimulus sugar composition at the time of testing.

The present study does not resolve the underlying question of whether liquids differ from solids in their satiating power. Past studies found no difference in satiating power between liquid cola and solid fat-free cookies (30) or between a drinkable liquid yogurt and the same yogurt that was eaten with a spoon (9). A review (20) showed that, whereas some studies found that liquids were less satiating than solids, other studies showed the opposite. Most recently, a study showing that apple juice had higher satiating power when it was called a "soup" attributed the difference to cognitive rather than physiologic factors (31).

In the present study, conducted with liquids only, a slightly but significantly different degree of compensation as compared with the no-beverage condition was obtained for 1%-fat milk only. This finding is of interest because 2 previous studies observed no differences in EIs among regular cola, orange juice, or 1%-fat milk, no matter whether the beverages were consumed 135 min before lunch (32) or with lunch (27). On the other hand, yogurts were associated with higher fullness ratings than were either dairy- or fruit-based drinks (9), possibly because of their higher protein content.

Although laboratory studies conducted with pure sugar solutions provide valuable data on fructose metabolism (12, 13), not all observations can be extrapolated to the human food supply. The hydrolysis of sucrose in soft drinks before consumption suggests that the substitution of HFCS for sucrose did not have the dramatic effects that had been claimed (2). The emerging view voiced in the scientific literature (33) and in the news media (34) is that any potential contribution of sugars to obesity is unlikely to be mediated by metabolic effects that are unique to HFCS.

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The authors' responsibilities were as follows—PM, MMP, and AD: study design and writing of the manuscript; PM and MMP: study implementation and data collection; PM, MMP, and AD: statistical analysis and revision of the dietary data. None of the authors had a personal or financial conflict of interest.

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<u>High Fructose Corn Syrup and Weight Gain</u>

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A Critical Examination of the Evidence Relating High Fructose Corn Syrup and Weight Gain

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The use of high fructose corn syrup (HFCS) has increased over the past several decades in the United States while overweight and obesity rates have risen dramatically. Some scientists hypothesize that HFCS consumption has uniquely contributed to the increasing mean body mass index (BMI) of the U.S. population. The Center for Food, Nutrition, and Agriculture Policy convened an expert panel to discuss the published scientific literature examining the relationship between consumption of HFCS or "soft drinks" (proxy for HFCS) and weight gain. The authors conducted original analysis to address certain gaps in the literature. Evidence from ecological studies linking HFCS consumption with rising BMI rates is unreliable. Evidence from epidemiologic studies and randomized controlled trials is inconclusive. Studies analyzing the differences between HFCS and sucrose consumption and their contributions to weight gain do not exist. HFCS and sucrose have similar monosaccharide compositions and sweetness values. The fructose:glucose (F:G) ratio in the U.S. food supply has not appreciably changed since the introduction of HFCS in the 1960s. It is unclear why HFCS would affect satiety or absorption and metabolism of fructose any differently than would sucrose. Based on the currently available evidence, the expert panel concluded that HFCS does not appear to contribute to overweight and obesity any differently than do other energy sources. Research recommendations were made to improve our understanding of the association of HFCS and weight gain.

Keywords body mass index, overweight, obesity, sucrose, fructose, glucose

INTRODUCTION

Overweight and obesity have become increasingly problematic in the United States from an individual and a population perspective. According to the body mass index (BMI) categories defined by the Centers for Disease Control and Prevention (CDC), about 65% of the U.S. adult population aged 20–74 years is currently overweight. In addition, 31% of all overweight adults are classified as obese. In 1976–80, only 47% and 15% of adults in the United States were considered overweight and obese, respectively (CDC, 2004). About 16% of American children and adolescents aged 6–19 years are also currently overweight. Two decades ago, about 6% of individuals in this age group were classified as overweight (CDC, 2004). Prior to 1976–80, such dramatic overweight and obesity rates were not observed in the United States.

Overweight and obese individuals are subject to societal stigmatization and are at increased risk for deleterious health conditions, including type 2 diabetes, cardiovascular diseases, hypertension, osteoarthritis, and some cancers (CDC, 2004). Overweight and obesity increase health care costs (USDA, 2004) and mortality rates (Mokdad et al., 2004, 2005; Flegal et al., 2005).

Overweight and obesity are influenced by many genetic and environmental contributors, including race/ethnicity, age, physical activity, sedentary behaviors, food consumption patterns, smoking, technological advancements, and psychological factors (CDC, 2004; Columbia Univ., 2000; Rashad and Grossman 2004). Researchers, government officials, politicians, and activist organizations are contributing significant resources in an

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attempt to understand and reduce the overweight and obesity "epidemic" in the United States.

All sources of energy consumed in excess of energy needs can contribute to increased BMI and risk of overweight and obesity. However, several arguments suggest that, in addition to providing energy, high fructose corn syrup (HFCS) may contribute to the development of overweight and obesity via other mechanisms. In the United States, HFCS has increasingly replaced refined sugar (sucrose) in many foods and most sweetened beverages. Outside the United States, HFCS is not used extensively, and sucrose continues to be the primary caloric sweetener.

Several types of HFCS—HFCS-42, HFCS-55, and HFCS-90—are produced by the food industry. Using enzymes to isomerize dextrose-based corn syrups, HFCS-42 was developed in the 1960s and contains 42% fructose, 53% glucose, and 5% higher saccharides. In the 1970s, the production of "supersweet" HFCS-90—containing 90% fructose, 9% glucose, and 1% higher saccharides—was made possible by passing HFCS-42 through an ion-exchange column. HFCS-55, which contains 55% fructose, 42% glucose, and 3% higher saccharides, was produced by blending HFCS-42 with HFCS-90 (Chaplin and Bucke, 1990; USDA, 2005; Hanover and White, 1993).

Sucrose, a disaccharide, is composed of two monosaccharides, fructose and glucose, in a ratio of 50:50. In sucrose, the monosaccharides are bound together in a covalent bond that is readily cleaved in the gastrointestinal tract by the enzyme sucrase. Although their monosaccharide compositions are very similar to sucrose, the monosaccharides in HFCS-42 and HFCS-55 are not covalently bonded; that is, their monosaccharides are free in solution. The major difference between sucrose and HFCS-42 and HFCS-55 is their percent moisture content (5% versus 29% and 23%, respectively) (Hanover and White, 1993).

The various formulations of HFCS have distinct applications within the food production industry. HFCS-42 is mainly used in baked goods, canned fruits, and condiments, while HFCS-55 is almost exclusively found in regular carbonated soft drinks (RCSD), other sweetened beverages (fruit drinks/ades), ice cream, and frozen desserts. In addition to its role in HFCS-55 production, HFCS-90 "is valued in natural and 'light' foods, where very little is needed to provide sweetness" (CRA, 2002).

Studies showing that the consumption of the monosaccharide fructose increases overall food intake, resulting in weight gain, are limited and occasionally contradictory. Some animal studies have found an association between fructose consumption and a reduction in food intake (Friedman, 1990). In humans, fructose absorption is facilitated by glucose and other monosaccharides, such as galactose. Excess fructose consumption by itself is known to cause gastric distress and osmotic diarrhea. The impact of fructose consumption on hormone levels, satiety, and subsequent short- and long-term food consumption is a complex relationship that deserves further study, a detailed discussion of which is beyond the scope of this review.

More importantly, the evidence from metabolism studies on fructose alone is irrelevant to the HFCS and weight gain debate. HFCS is not fructose. HFCS is compositionally similar to sucrose. The fructose concentrations used in most fructose metabolism studies greatly exceed the daily fructose consumption of the average American. Even if it were established that consuming fructose leads to over-consumption and weight gain, this would not imply that consuming HFCS also leads to over-consumption and weight gain.

Recently, several hypotheses concerning the causes of overweight and obesity have centered on HFCS. These hypotheses imply that HFCS is unique in its contribution to overweight and obesity beyond being a source of energy. In addition, because soft drinks are consumed by diverse age, socioeconomic, and race/ethnic groups in the United States, soft drink consumption is often utilized as a "proxy" of overall HFCS consumption in studies examining overweight and obesity in the United States.

The Center for Food, Nutrition, and Agriculture Policy convened an expert panel to critically and thoroughly examine the existing evidence linking HFCS consumption to changes in BMI and body weight. The objective of the expert panel was to assess the strength of the evidence for the role of HFCS as a unique contributor to an increased risk of overweight and obesity.

METHODOLOGY

A thorough literature search was conducted using PubMed. Medical subject heading (MeSH) key words used to search the database included: high fructose corn syrup, obesity, sucrose, and beverages. Several types of studies were identified from the search including literature reviews, commentaries, ecological and epidemiologic studies, randomized controlled trials (RCTs), and animal studies. We utilized the ISI *Web of Science*® to identify widely-cited scientific publications to discuss in detail in this manuscript. Recently published studies were included based on the professional judgment of the panel.

ARGUMENTS CONSIDERED

Several arguments have been proposed suggesting that HFCS warrants special attention for the prevention of overweight and obesity because this sweetener has specific properties that uniquely contribute to weight gain. We have organized and summarized these arguments using diagrams (Figs. 1–2). Figure 1 contains a conceptual overview of the arguments. The figure attempts to summarize the major lines of argument and indicate the evidence that would be necessary to support it. Rounded boxes show the beginning and end points of an argument, rectangular boxes indicate an action or process, rectangular boxes with two extra vertical lines designate a sub-process, and non-rectangular parallelograms indicate a proxy. Recurring proxies for HFCS throughout the scientific literature are the various classifications of "soft drinks." The question mark symbol indicates that data is currently not sufficient to support the proposed claim. Figure 2 details the theoretical mechanisms referred to in Fig. 1. Arrows specify the argument flow and the stages at which evidence is required in order to support the argument. If contradictory evidence is available at any point along the path to weight gain, the argument for that particular path is rendered invalid. Any

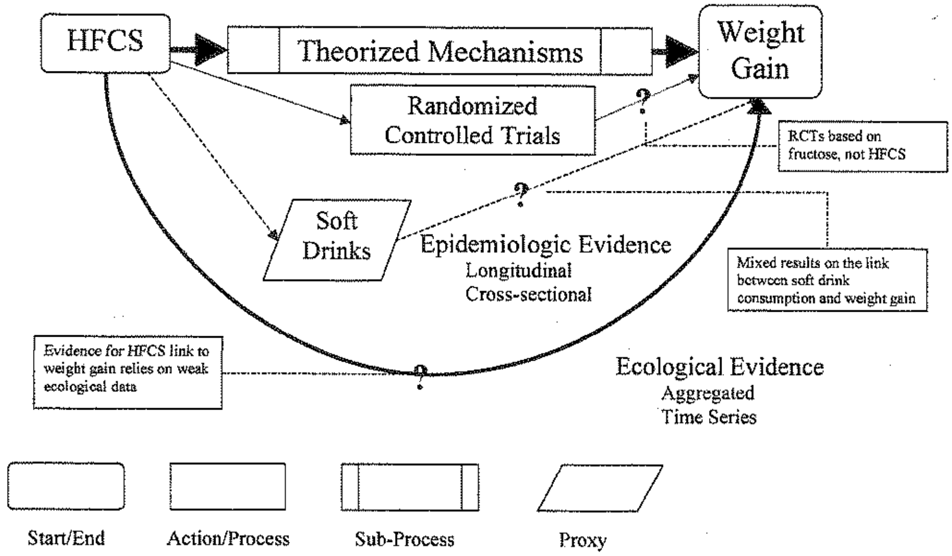

Figure 1 Conceptual overview of the proposed arguments supporting the relationship between high fructose corn syrup (HFCS) consumption and weight gain. Rounded boxes show the beginning and end points of an argument; rectangular boxes indicate an action or process; rectangular boxes with two extra vertical lines designate a sub-process; non-rectangular parallelograms indicate a proxy. Recurring proxies for HFCS throughout the scientific literature are the various classifications of "soft drinks." Arrows specify the argument flow and the stages at which evidence is required in order to support the argument. The question marks indicate that data is currently not sufficient to support the proposed claim. Figure produced by authors.

of the ensuing sub-processes are irrelevant if a line of argument has been shown to be invalid, regardless of whether or not the ensuing sub-processes have been technically validated by other evidence. Once the chain of logic has been broken, the argument is no longer valid. Although lack of evidence does not invalidate an argument, it does make the truth of an argument indeterminate.

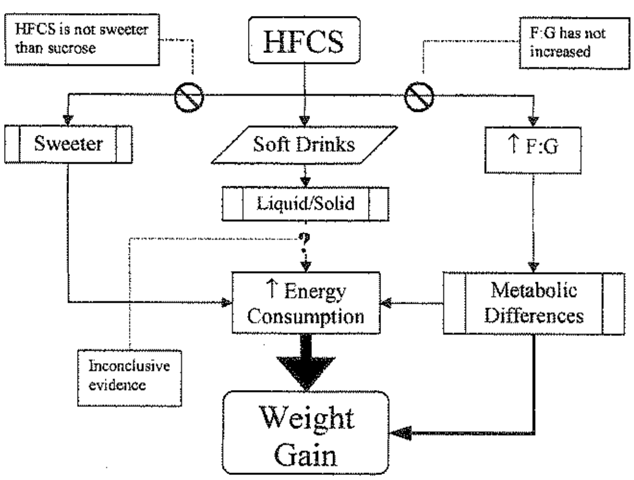

Figure 2 Conceptual overview of the theorized mechanisms supporting the relationship between high fructose corn syrup (HFCS) consumption and weight gain. Rounded boxes show the beginning and end points of an argument; rectangular boxes indicate an action or process; rectangular boxes with two extra vertical lines designate a sub-process; non-rectangular parallelograms indicate a proxy. Recurring proxies for HFCS throughout the scientific literature are the various classifications of "soft drinks." Arrows specify the argument flow and the stages at which evidence is required in order to support the argument. The not symbol (⃠) indicates that evidence that contradicts the claim is available. The question mark indicates that data is currently not sufficient to support the proposed claim. Figure produced by authors.

Figure 1 illustrates the hypothesis that HFCS consumption is positively associated with weight gain via one or more theorized mechanisms. Two types of studies—ecological and epidemiologic—have been extensively cited in support of this relationship. Epidemiologic studies typically utilize various classifications of "soft drinks" as a proxy for HFCS in an attempt to evaluate a putative link between HFCS consumption and weight gain. A small number of randomized controlled trials have also examined the association between "soft drink" consumption and weight gain.

Figure 2 provides further detail of the theorized mechanisms linking HFCS consumption and weight gain. According to discussions in the scientific literature, there are three possible mechanisms: 1) HFCS is "sweeter" than sucrose, leading to greater energy consumption and weight gain, 2) humans do not compensate for excess energy provided by soft drinks (HFCS proxy), leading to greater energy consumption and weight gain, and 3) increased levels of HFCS in the food supply has increased the fructose:glucose (F:G) ratio of the American diet, causing adverse metabolic effects that either directly or indirectly (via greater energy consumption) lead to weight gain. It has been argued that increasing the F:G ratio may: 1) increase hepatic lipogenesis, leading to increased fat production and weight gain, and/or 2) decrease the release of the satiety hormones insulin and leptin and increase the release of the hunger hormone ghrelin, leading to greater energy consumption and weight gain. The not symbol (⃠) indicates that evidence that contradicts the claim is available.

In the following sections, we will review the ecological and epidemiologic studies and the RCTs that directly or indirectly address the relationship between HFCS consumption and risk of overweight and obesity. The details of the studies are presented in Tables 1–4, identifying the type of study and data used, a summary of the results, and any remarks from the authors of this review. In addition, we will also address the feasibility of each of the theorized mechanisms outlined above.

Table 1 Review of ecological studies on the association between HFCS and weight gain

Study	Type of Analysis	Summary of Results	Remarks
Gross et al., 2004.	Ecological Per capita nutrient consumption data from the U.S. Department of Agriculture (USDA) and type 2 diabetes prevalence data from the CDC	From 1909 to 1997, the incidence of type 2 diabetes was significantly and positively associated with per capita intakes of fat ($r = 0.84$; $P < 0.001$), total carbohydrate ($r = 0.55$; $P < 0.001$), protein ($r = 0.71$; $P < 0.001$), fiber ($r = 0.16$; $P = 0.027$), corn syrup ($r = 0.83$; $P < 0.001$), and total energy ($r = 0.75$; $P < 0.001$). Multivariate nutrient-density model found that the percent of total energy contributed by corn syrup was positively associated ($b = 0.0132$; $P = 0.038$), and the percent of total energy contributed by fiber was negatively associated ($b = -13.86$; $P < 0.01$), with the incidence of type 2 diabetes.	"Corn syrup" is used inappropriately by Gross et al. "Corn syrup" (ACH Food Co., 2003) is a corn-based sweetener containing various amounts of glucose (dextrose), maltose, isomaltose, maltotriose, and higher molecular weight saccharides. (Chaplin and Bucke, 1990) Unlike corn syrups, HFCS contains fructose in addition to other saccharides. (Hanover and White, 1993)
Harnack et al., 2000.	Ecological Per capita nutrient and energy availability in the United States between 1976–80 and 1988–94 Food and nutrient data from various agriculture, business, and medical databases	The authors observed a decline in per capita availability for seven food categories and an increase in per capita availability for 17 food categories, one of which was corn sweeteners (283.4%). They also noted that the increase in per capita availability of total energy during this time period coincided with the increase in the percentage of overweight children, adolescents, and adults. The per capita availability of many other foods, such as 1% milk (423.8%), poultry (84.5%), and frozen vegetables (72.9%), also increased substantially during this time period.	The ecological data are insufficient to determine which trends, if any, are independently associated with rising overweight and obesity rates. Harnack *et al.* did not directly evaluate the association between BMI values and intake of either total energy or specific macronutrients.
Nielsen and Popkin, 2004.	Ecological Analyzed data from the Nationwide Food Consumption Survey (NFCS) 1977–78 ($n = 29{,}695$), the Continuing Survey of Food Intake for Individuals (CSFII) 1989–91 ($n = 14{,}658$), CSFII 1994–96, 98 ($n = 19{,}027$), and the National Health and Nutrition Examination Survey (NHANES) 1999–2001 ($n = 9965$) to determine consumption trends of specific beverages among all individuals aged ≥ 2 years.	Survey participants were divided into four age categories: 2–18 years, 19–39 years, 40–59 years, and ≥ 60 years. Nielsen and Popkin reported that sweetened beverage (soft drinks plus fruit drinks) consumption increased for all age groups between 1977–78 and 1999–2001 with an overall 135% increase in energy intake from sweetened beverages.	The authors presented no data supporting any relationship between overweight and obesity and the consumption of soft drinks or fruit drinks.
Popkin and Nielsen, 2003.	Ecological Analyzed associations between caloric sweetener consumption trends, percent urbanization, and per capita gross national product (GNP) in multiple countries. Analyzed food-disappearance data to estimate caloric sweetener consumption from 103 countries in 1962 and from 127 countries in 2000.	These authors found a 74 kcal/person increase in per capita caloric sweetener availability between 1962 and 2000. Using pooled regressions from 1962 and 2000, Popkin and Nielsen attributed about 82% of the increase in caloric sweetener consumption to GNP and urbanization shifts. They credited the remaining 18% increase in caloric sweetener consumption to unmeasured factors, such as changes in food production and/or consumer behavior.	These authors only addressed trends in worldwide caloric sweetener consumption. No assessment of the relationship between caloric sweetener consumption and overweight and obesity was undertaken.

Table 2 Review of cross-sectional epidemiologic studies on the association between HFCS and weight gain

Study	Type of Analysis	Summary of Results	Remarks
Forshee and Storey, 2003.	Cross-Sectional Utilized CSFII 1994–96, 98 to examine consumption patterns of non-water beverages [milk, fruit juices, regular fruit drinks/ades, diet fruit drinks/ades, regular carbonated soft drinks (RCSD), and diet carbonated soft drinks (DCSD)] among 1749 children (6–11 years) and adolescents (12–19 years).	After controlling for age, race/ethnicity, and family income, these authors found that BMI had a statistically significant and positive relationship with DCSD consumption for both boys ($p < 0.05$) and girls ($p < 0.05$). Since DCSD contains little, if any, energy, these beverages were most likely a marker, not a cause, of higher BMI values among study participants. Overweight children are more likely to consume DCSD in an attempt to control or decrease their weight. BMI did not show an association with RCSD or fruit drink/ade consumption.	Study limitations include no controls for sedentary behaviors, physical activity, and intake of energy from sources other than beverages in the model. In addition, BMI and beverage consumption were self-reported and subject to measurement error. Causal inferences cannot be made from cross-sectional study designs.
Forshee et al. (2004).	Cross-sectional Utilized data from NHANES 1988–94 in order to examine the relative association of demographic variables, beverage consumption, physical activity, and sedentary behaviors with BMI for 2216 adolescents aged 12–16 years. Separate analyses of the dietary assessment tools—one 24-hour dietary recall (24HR) and one food frequency questionnaire (FFQ)—included in NHANES 1988–94. In order to control for total energy, energy from sources other than beverages was calculated ($E_{Other} = E_{Total} - E_{Bev}$) and included in the 24 HR and the FFQ models.	In the 24 HR multivariate regression model, consumption of DCSD ($b = 0.0041$; 95% CI = 0.0007 to 0.0074) was positively associated with BMI for females ($p < 0.05$). Neither RCSD nor fruit drinks/ades were associated with BMI for females or males. In the FFQ multivariate regression model, consumption of DCSD ($b = 0.0408$; 95% CI = 0.0169 to 0.0647) was positively associated with BMI for females ($p < 0.05$). No relationship was observed between any other beverage consumption category and BMI for either females or males.	Since food and beverage consumption, physical activity, and television viewing were self-reported, these variables are subject to measurement error. In addition, by truncating television viewing at a maximum of 5 hours/day, an artificial ceiling was imposed on this variable. Causal inferences cannot be made from cross-sectional study designs.
French et al. 2003.	Cross-sectional Analyzed soft drink consumption trends among children aged 6–17 years. Soft drinks were defined as "carbonated beverages (all United States Department of Agriculture database codes starting with 924) and included flavored waters and juice drinks." (French et al., 2001). Data were obtained from NFCS 1977–78 (n = 8908) and CSFII 1994–96, 98 (n = 3177).	The overall prevalence of soft drink consumption among children aged 6–17 years was 48% higher in 1994–96, 98 than in 1977–78. Mean soft drink intake increased from 5 to 12 oz/day (155 to 370 g/day).	The relationship between soft drink consumption and BMI was not examined. Causal inferences cannot be made from cross-sectional study designs.
Giammattei et al. (2003).	Cross-sectional Investigated the relationship between BMI, television viewing, and regular and diet soft drink consumption among non-diabetic sixth and seventh grade non-Hispanic white (n = 188), Latino (n = 167), and Asian (n = 30) students from 3 different schools in Santa Barbara County, California. Of these 385 children, 305 children completed a questionnaire of 18 lifestyle questions.	Found that 17.9% of the students were at-risk of overweight (BMI ≥85th and <95th percentile), while 17.4% of the students were overweight (BMI ≥95th percentile). Only the number of hours of television viewing on a school night and the total number of soft drinks consumed per day were significantly associated with BMI. When regular and diet soft drinks were analyzed separately, BMI z-scores ($P = 0.001$) and percent body fat ($P = 0.0002$) remained positively and significantly associated with diet soft drink consumption only. BMI z-scores ($P = 0.08$) and percent body fat ($P = 0.06$) were not significantly associated with regular soft drink consumption.	Since the study was limited to sixth and seventh grade students from 3 schools in Santa Barbara County, California, the generalizability of this study to other students is limited. Casual inferences cannot be made from cross-sectional study designs.
Grant et al. (2004).	Cross-sectional Studied the relationship between anthropometric status and macronutrient intake among Pacific Island children aged 2–5 years living in New Zealand.	Of the 56 children who provided height, weight, and 2-day food records, 32 were classified as obese (BMI ≥95th percentile) and 24 were classified as non-obese (BMI <95th percentile).	Consumption of foods and beverages sweetened with HFCS is very limited in New Zealand since HFCS is almost exclusively produced and consumed within the United States. However,

(Continued on next page)

Table 2 Review of cross-sectional epidemiologic studies on the association between HFCS and weight gain *(Continued)*

Study	Type of Analysis	Summary of Results	Remarks
	Classified children with a BMI ≥95th percentile of the CDC's BMI-for-age tables as obese.	After adjusting for age and gender, the obese children consumed significantly more total energy than did the non-obese children ($P < 0.05$). The obese children consumed more of all types of foods, not just more of specific foods, than did the non-obese children. Percent of total energy obtained from fat, carbohydrate, sugars, and sucrose was not significantly different between the obese and non-obese children.	Grant et al. did evaluate the relationship between sucrose, which has a monosaccharide composition similar to that of HFCS-42 and HFCS-55, and obesity. The study did not control for physical activity. Causal inferences cannot be made from cross-sectional study designs.
Nicklas et al. (2003).	Cross-sectional Analyzed the relationship between BMI and food consumption patterns among 1562 African-American (AA) and Euro-American (EA) 10-year-olds in Bogalusa, Louisiana between 1973 and 1994 (The Bogalusa Heart Study). Combined the children at-risk for overweight (BMI ≥ 85th and <95th percentile) with the overweight children (BMI ≥ 95th percentile) into one overweight group.	After controlling for total energy intake, age, study year, ethnicity, gender, and ethnicity-gender interaction, the authors found positive associations between overweight and consumption (in grams) of total foods and beverages (OR = 1.77; $p < 0.05$), snacks (OR = 1.24; $p < 0.05$), and low-quality foods (OR = 1.35; $p < 0.01$). Food consumption patterns that included consumption of sweets (OR = 1.38; $p < 0.05$) and sweetened beverages (OR = 1.33; $p < 0.001$) were also associated with overweight. After analyzing the association between food consumption patterns and overweight status by ethnicity-gender groups, only EA males and EA females showed positive associations between overweight and consumption of sweets ($p < 0.05$ for both) and sweetened beverages ($p < 0.01$ for males; $p < 0.05$ for females). For EA males and EA females, positive associations were also found between overweight and consumption of total foods and beverages ($p < 0.05$ for both), particularly from low-quality foods ($p < 0.05$ for both). A positive association between overweight and consumption of the dinner meal ($p < 0.05$) was observed for EA males only. AA females showed negative associations between overweight and consumption of fruits/fruit juices ($p < 0.01$) and fruit/fruit juices/vegetables ($p < 0.01$), total number of meals consumed ($p < 0.05$), and consumption of the breakfast meal ($p < 0.05$). The model explained about 4–8% of the variance in BMI for the various ethnic-gender groups, and soft drink consumption alone explained approximately 1% of the variance in the model.	The results from the Nicklas *et al.* study must be interpreted with caution because none of the models examining associations among eating-pattern variables and overweight status controlled for physical activity. Causal inferences cannot be made from cross-sectional study designs.
Rajeshwari et al. (2005).	Cross-sectional Bogalusa Heart Study Analysis of the relationships between sweetened-beverage consumption and BMI, total energy intake, and milk consumption All sweetened-beverages were assigned to one of the following categories: soft drinks, fruit drinks, iced tea with sugar, and coffee with sugar. Study participants were categorized as either non-consumers, low-consumers, medium-consumers, or high-consumers of sweetened-beverages.	Between 1973 and 1994, mean BMI significantly increased for each of the four sweetened-beverage consumption categories, but there were no differences in mean BMI among any of the four consumption categories. Only the medium-consumers ($p < 0.001$) and high-consumers ($p < 0.001$) of sweetened-beverages significantly increased their mean gram consumption during this time period.	The results from this study must be interpreted with caution due to regional variations in sweetened-beverage consumption patterns among children. The models did not control for physical activity. Causal inferences cannot be made from cross-sectional study designs.

Table 2 Review of cross-sectional epidemiologic studies on the association between HFCS and weight gain *(Continued)*

Study	Type of Analysis	Summary of Results	Remarks
Zizza et al. (2001).	Cross-sectional Data from NFCS 1977–78 (n = 4472), CSFII 1989–91 (n = 2373), and CSFII 1994–96 (n = 1648). Analyzed snacking trends among individuals aged 19–29 years	Sweetened beverages (regular soft drinks, diet soft drinks, and fruit drinks) were one of the major contributors of energy from snacking occasions. Overall snacking prevalence increased from 77% in 1977–78 to 84% in 1994–96. Energy consumed per snacking occasion increased by 26%, while the number of snacks consumed per day increased by 14%.	The relationship between snacking and BMI was not examined. The models did not control for physical activity. Causal inferences cannot be made from cross-sectional study designs.

ECOLOGICAL EVIDENCE

Overview

Ecological (population) studies use aggregate data to describe relationships between substance exposure and some other variable (e.g. disease) either among several populations over different geographical areas or within one population over several time periods (Coggon et al., 1997; CDC, 2005). Ecological studies produce the weakest evidence linking substance exposure and health outcomes because ecological studies are highly susceptible to bias, confounding, and chance (CDC, 2005; Robinson, 1950; Greenland and Morgenstern, 1989, 1991). Relative to other study designs, ecological studies are less expensive and time-consuming, yet they can not establish cause-effect relationships or even individual-level associations. Ecological studies can be useful tools to generate hypotheses for later testing by rigorous analysis (CDC, 2005). Spurious relationships, often called "ecological fallacies," can result from using aggregate data to imply cause-effect relationships (Morgenstern, 1995; King, 1997).

Because the data points are averages and not individuals, it is impossible to determine whether a higher consumption of particular foods or food ingredients by individuals is associated with higher BMI values for those individuals. It has even been shown that the correlation between two variables using averages may be the opposite sign of the correlation between the same two variables measured among individuals. For example, Robinson reported in 1950 that the individual correlation of being foreign born and illiteracy was 0.118, but when aggregated to percentages by state, the correlation was −0.526 (Robinson, 1950). Relying on the correlation produced by aggregated data would have given the wrong answer by a large margin. The same type of error may occur when using average food consumption data to explain average BMI data.

Additionally, ecological data are usually small samples. Statistical models need to control for all potential confounding factors or the results will be biased. For a complex problem like obesity, this typically means that you need hundreds or thousands of data points to have sufficient statistical power while controlling for all of the reasonable potential confounding variables. In this case, U.S. per capita HFCS consumption data are available only from 1967 to 2003 for a total of 37 data points (USDA, 2004). These are far too few data points to properly control for the dozens of societal changes that may have been associated with changes in obesity prevalence over the past four decades.

Literature Review of the Ecological Studies

Four widely cited ecological studies that hypothesize a relationship between HFCS consumption and weight gain were found in the scientific literature.

Gross et al. (2004), using per capita nutrient consumption data from the U.S. Department of Agriculture (USDA) and type 2 diabetes prevalence data from the CDC, examined the relationship between the consumption of refined carbohydrates and the incidence of type 2 diabetes—a disease strongly linked to overweight and obesity (CDC, 2004). According to their initial analyses of the available data from 1909 to 1997, the incidence of type 2 diabetes was significantly and positively associated with per capita intakes of fat, total carbohydrate, protein, fiber, corn syrup, and total energy. When the study authors utilized a multivariate nutrient-density model, the percent of total energy contributed by corn syrup was positively associated and the percent of total energy contributed by fiber was negatively associated with the incidence of type 2 diabetes.

Harnack et al. (2000) observed a decline in per capita availability for seven food categories and an increase in per capita availability for 17 food categories, one of which was corn sweeteners. They also noted that the increase in per capita availability of total energy during this time period coincided with the increase in the percentage of overweight children, adolescents, and adults. The per capita availability of many other foods, such as 1% milk, poultry, and frozen vegetables also increased substantially during this time period. Harnack et al. did not directly evaluate the association between BMI values and intake of either total energy or specific macronutrients.

Nielsen and Popkin (2004) reported that sweetened beverage (soft drinks plus fruit drinks) consumption increased for all age groups between 1977–78 and 1999–2001 with an overall 135% increase in energy intake from sweetened beverages. The relationship between beverage consumption and BMI was not examined.

Popkin and Nielsen (2003) found a large increase in per capita caloric sweetener availability between 1962 and 2000,

Table 3 Review of longitudinal epidemiologic studies on the association between HFCS and weight gain

Study	Type of Analysis	Summary of Results	Remarks
Berkey et al., 2004.	Longitudinal U.S. Growing Up Today Study (GUTS) Analyzed the relationship between BMI and intakes of sugar-added beverages, milk, fruit juices, and diet soda in a cohort of more than 10,000 males and females aged 9-14 years in 1996.	Positive association between BMI and sugar-added beverage consumption for boys ($p = 0.038$), but the association was not statistically significant for girls ($p = 0.096$). For each serving of sugar-added beverages consumed per day, BMI increased by 0.028 kg/m^2 for boys and by 0.021 kg/m^{2}for girls from the previous year. When total energy was included in the model, the associations were not significant for either boys ($p = 0.317$) or girls ($p = 0.167$).	This study found no statistically significant association between sugar-added beverage consumption and BMI after controlling for total energy. The data are not nationally representative. The study used self-reported data that may be subject to measurement error.
Field et al., 2004.	Longitudinal GUTS Investigated the association between BMI and the intake of various snack foods, including sugar-sweetened beverages.	After controlling for a variety of potential confounders, including total energy intake, no relationship was found between snack food intake and annual change in BMI for either girls ($b = -0.006$) or boys ($b = -0.004$). According to these authors, "[w]hen servings per day of sugar-sweetened beverages were included as snack foods the association between snack food intake and change in BMI z-score was similar to the main findings" (Field et al., 2004) for girls (b = -0.004) and boys (b = -0.003).	This study found no association between snack food consumption (including sugar-sweetened beverages) and BMI. The data are not nationally representative. The study used self-reported data that may be subject to measurement error.
Ludwig et al., 2001.	Longitudinal A cohort of 548 ethnically diverse schoolchildren aged 11–12 years enrolled in Massachusetts public schools Examined the relationship between BMI and consumption of sugar-sweetened drinks Changes in BMI and sugar-sweetened drink consumption were measured for 19 months.	Average sugar-sweetened drink consumption increased from 1.22 to 1.44 servings/day—a difference of 0.22 servings/day. After controlling for baseline anthropometrics and demographics, dietary variables, physical activity, television viewing, and total energy intake, the estimated association of sugar-sweetened drinks with BMI was a 0.24 kg/m^2 increase in BMI for each additional serving/day increase in sugar-sweetened drink consumption ($p = 0.03$).	For the average increase in sugar-sweetened drink consumption (0.22 servings/day), this model predicted an annual BMI increase of 0.05 kg/m^2 assuming all other variables in the model remained constant. Nielsen and Popkin (2004), reported that between 1977 and 1996, mean consumption of sweetened beverages increased from 2.02 to 2.55 servings/day for a mean increase of 0.53 servings/day. Using the Ludwig et al. estimate, the predicted increase in BMI would be 0.13 kg/m^2 for an increase of 0.53 servings/day of sugar-sweetened drink consumption [(0.53 servings/day)(0.24 kg/m^2/servings/day)]. The data are not nationally representative.
Newby et al., 2004.	Longitudinal North Dakota Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). Cohort of 1345 children aged 2-5 years visited WIC clinics at least twice between January 1995 and June 1998. Explored the relationship between beverage consumption and changes in BMI	Found no significant relationships between any of the beverages analyzed and BMI. When soda was analyzed separately, an increase in soda consumption of 1 oz/day (31 g/day) predicted a non-significant decrease of 0.01 ± 0.02 BMI units (kg/m^2)/year ($P = 0.50$). When all beverages were included in the model, an increase in soda consumption of 1 oz/day (31 g/day) predicted an identical BMI unit/year decrease ($P = 0.58$).	This study found no relationship between soda consumption and the BMI values of young children. The data are not nationally representative. The study used self-reported data that may be subject to measurement error.
Schulze et al., 2004.	Longitudinal Nurses' Health Study II Cohort of 51,603 females Examined the relationship between sugar-sweetened beverage consumption, weight change, and risk of type 2 diabetes.	After controlling for a wide range of potential confounders including physical activity, smoking, other components of the diet, and other variables, between 1991 and 1995, those individuals whose sugar-sweetened beverage consumption remained consistent at either ≤ 1 drink/week (n = 38,737) or ≥ 1 drink/day (n = 2366) increased in weight by	More than half of the respondents in the Nurses' Health Study II were excluded from the Schulze *et al.* analysis because of various exclusion criteria. The mean change in sugar-sweetened beverage consumption for the low-high (≤ 1 drink/week to ≥ 1 drink/day) consumption category was significantly different from the mean change for the

Table 3 Review of longitudinal epidemiologic studies on the association between HFCS and weight gain *(Continued)*

Study	Type of Analysis	Summary of Results	Remarks
		3.21 kg/4 years (1.8 lb/year) and 3.12 kg/4 years (1.7 lb/year), respectively. Those individuals with the greatest decrease (≥1 drink/day to ≤1 drink/week; n=1020) or increase (≤1 drink/week to ≥1 drink/day; n = 1007) in their sugar-sweetened beverage consumption experienced a weight increase of 1.34 kg/4 years (0.7 lb/year) and 4.69 kg/4 years (2.6 lb/year), respectively. The remaining individuals whose sugar-sweetened beverage consumption patterns did not fit these four consumption categories were classified by the study as "Other." This would include, for example, individuals who consistently consumed 2-6 drinks/week or who switched from ≥1 drink/day to 2-6 drinks/week. The "Other" category included 16% of the cohort population, and the average weight increase for this category was 3.04 kg/4 years (1.7 lb/year). The cohort was also studied from 1995 to 1999. During this time, individuals who consistently consumed ≤1 drink/week (n = 39,279) or ≥1 drink/day (n = 2340) gained an average of 2.04 kg/4 years (1.1 lb/year) and 2.21 kg/4 years (1.2 lb/year), respectively. Those individuals with the greatest decrease (≥1 drink/day to ≤1 drink/week; n = 1107) or increase (≤1 drink/week to ≥1 drink/day; n = 765) in their sugar-sweetened beverage consumption gained an average of 0.15 kg/4 years (0.1 lb/year) and 4.20 kg/4 years (2.3 lb/year), respectively. Those in the "Other" category gained an average of 2.10 kg/4 years (1.2 lb/year) and included 16% of the cohort population.	low-low (consistent at ≤1 drink/week), high-high (consistent at ≥1 drink/day), and high-low (≥1 drink/day to ≤1 drink/week) consumption categories (*P* < 0.001). The low-high consumption category only contained about 2% of the study sample. About 75% of the study sample was located in the low-low consumption category, and about 5% of the study sample was located in the high-high consumption category. The results of the study suggest that those individuals in the high consumption category could benefit by reducing their consumption to ≤1 drink/week and that those individuals in the low consumption category could benefit by limiting their increase to no more than 2–6 drinks/week. Smaller changes in sweetened beverage consumption did not show any differences in weight gain.
Janket et al., 2003.	Longitudinal/RCT Women's Health Study (WHS) Cohort of 38,480 female health professionals aged ≥45 years Only included participants from the WHS who had completed FFQs and had no history of diabetes at baseline Examined the relationship between risk of type 2 diabetes and intakes of total caloric sweeteners, sucrose, fructose, glucose, and lactose During follow-up, 918 cases of type 2 diabetes were identified.	After controlling for age, smoking, BMI, vigorous exercise, alcohol use, history of hypertension and high cholesterol, post-menopausal hormone and vitamin use, and family history of type 2 diabetes, the authors found no association between the lowest versus highest consumption categories of total caloric sweeteners, sucrose, fructose, glucose, or lactose and risk of type 2 diabetes.	Neither fructose nor glucose—the main components of HFCS—were related to the risk of developing type 2 diabetes. Sucrose, which has a F:G ratio very similar to that of HFCS, was also not related to the risk of developing type 2 diabetes. The data are not nationally representative. The study used self-reported data that may be subject to measurement error.
Mrdjenovic and Levitsky, 2003.	RCT Examined the effects of excessive sweetened drink consumption [defined as >12 oz (>370 g)/day] on total energy intake and weight gain among 30 children aged 6–13 years attending the Cornell Summer Day Camp in 1997 All children consumed home-prepared foods during the first week of camp.	Children who consumed >16 oz/day (>492 g/day) of sweetened drinks gained more weight (1.12 ± 0.7 kg) than did children who consumed between 6 and 16 oz/day (186 and 492 g/day) of sweetened drinks (0.32 – 0.48 ± 0.4 kg). In addition, children who consumed >12 oz/day (>370 g/day) of fruit juice gained more weight (3.3 ± 1.95 kg) than did	Average daily intake of total energy did not exceed the Recommended Daily Allowance (RDA) for any of the age groups in the study. Children in the highest and lowest sweetened drink consumption categories had daily total energy intakes of 91% ± 5% and 82% ± 5% of the RDA, respectively. In addition, children between the ages of 6

(Continued on next page)

Table 3 Review of longitudinal epidemiologic studies on the association between HFCS and weight gain *(Continued)*

Study	Type of Analysis	Summary of Results	Remarks
	From the second week of camp to the end of the study, each child was provided meals and snacks prepared by study administrators for consumption at camp (breakfast, lunch, and two snacks) or at home (dinner). Three beverage categories were included in the analysis—milk (fluid milk and milk shakes), 100% fruit juice, and sweetened drinks (carbonated fruit-flavored drinks, noncarbonated fruit-flavored drinks, less than 100% fruit juice, sodas, and tea). Daily beverage consumption was divided into four categories—0 [no drink consumed (0 g/day)], 1 [no more than 6 oz (186 g)], 2 [between 6 and 12 oz (186 and 370 g)], 3 [>12 but <16 oz (>370 but <492 g)], and 4 [>16 oz (>492 g)]. Daily dietary intakes were collected over 4 to 8 weeks. Body weights and heights were measured either after the first week of camp or on the first day the child joined the study. Second weight measurements were recorded during a child's final week at camp and were not obtained for all study participants (n = 21). The study authors did not discuss or include second height measurements in their study.	children who consumed <6 oz/day (<186 g/day) of fruit juice (0.5 ± 0.4 kg). None of these differences was statistically significant, and the authors observed that "the sample size was too small (n = 21) to provide sufficient power for the observed difference in weight gain to be statistically significant." Mrdjenovic and Levitsky, 2003. It is also possible that the observed difference in weight gain was not significant due to the absence of a relationship between sweetened drink consumption and weight gain.	and 13 years are increasing in height as well as weight. BMI, which accounts for the relationship between height and weight, would have been a better measure of the relationship between sweetened drink consumption and weight gain due to increased adiposity. The models did not control for physical activity. The study had a small sample size (n = 30 total, n = 21 for a second weight measurement) that was not nationally representative.

during which daily caloric sweetener consumption increased by 74 kcal/person. They attributed about 82% of the increase in caloric sweetener consumption to GNP and urbanization shifts. They credited the remaining 18% increase in caloric sweetener consumption to unmeasured factors, such as changes in food production and/or consumer behavior. No assessment of the relationship between caloric sweetener consumption and overweight and obesity was undertaken.

Table 4 Review of randomized controlled trials on the association between HFCS and weight gain

Study	Type of Analysis	Summary of Results	Remarks
James et al., 2004	Cluster RCT Focused educational intervention program on carbonated drink consumption and overweight and obesity in 644 children aged 7–11 years The children were recruited from six primary schools in southwest England and assigned to one of the 29 study clusters which were each randomly assigned to the intervention or control group. Children in the intervention clusters participated in a program designed to emphasize the consumption of a balanced healthy diet and to discourage the consumption of both sweetened and unsweetened "fizzy" drinks. Included anthropometric measurements taken at six-month intervals and 3-day dietary records (two weekdays and one weekend) obtained at baseline and at the end of the trial.	Observed a decrease in carbonated drink consumption of 0.6 glasses/3 days (50 ml/day) in the intervention group with an increase in carbonated drink consumption of 0.2 glasses/3 days (17 ml/day) in the control group. Mean percentage of overweight and obese children decreased by 0.2% in the intervention group and increased by 7.5% in the control group. The percent difference of overweight and obese children between the intervention and control groups was statistically significant (7.7%; 95% CI = 2.2% to 13.1%). Differences in average BMI values (0.1 kg/m^2; 95% CI = -0.1 kg/m^2 to 0.3 kg/m^2) and z-scores (0.04; 95% CI = -0.04 to 0.12) between the intervention and control groups were not statistically significant.	Because only the United States produces carbonated drinks sweetened with HFCS, the sweetened "fizzy" drinks in this study were most likely sweetened with sucrose. The data are not nationally representative.

Summary of the Ecological Studies

None of the reviewed ecological studies investigated the relationship between HFCS availability in the food supply and population BMI values. Gross et al. also inappropriately used the term "corn syrup" in their analysis. HFCS, composed mainly of fructose and glucose, is a sweetener derived from corn that is widely used in commercial food production. The term "corn syrup," which many individuals equate with Karo® Syrup, is an entirely glucose-based corn sweetener that was developed for use in the home. Other glucose-based corn sweeteners are produced for use in commercial food production. However, unlike HFCS, their per capita consumption has remained relatively unchanged since 1966 (USDA, 2004). Harnack et al. examined trends in the availability of corn sweeteners, which presumably included the glucose-based corn sweeteners in addition to HFCS, but they did not examine the relationship between corn sweeteners and BMI. Nielsen and Popkin analyzed soft drink and fruit drink consumption trends and did not examine their relationship with BMI. Popkin and Nielsen investigated caloric sweeteners, which could include sucrose, glucose, fructose, HFCS, and other saccharides, but did not estimate the relationship between caloric sweeteners and BMI.

Current ecological studies neither support nor invalidate a hypothesized relationship between HFCS availability and BMI. The increase in BMI values in the U.S. population since the 1970s may have originated from any number of concurrent trends, such as, but not limited to, changes in energy intake from a variety of food sources (Harnack et al., 2000), an increase in sedentary occupations (Lakdawalla and Philipson, 2002), an increase in workforce participation among women (Anderson et al., 2003; Crepinsek and Burstein, 2004), and a decrease in physical education (PE) classes and extracurricular sports programs in schools (Andersen et al. 1998).

EPIDEMIOLOGIC EVIDENCE

Overview

Epidemiological research can include longitudinal, cross-sectional, and case-control studies. Each type has well-known strengths and limitations (Coggon et al., 1997, 1997, 1997). Our literature search found longitudinal and cross-sectional studies that directly or indirectly examined the relationship between HFCS consumption and the prevalence of overweight and/or obesity. No case-control studies on this relationship were found.

Many studies described in this section use the term "sugar-sweetened" soft drinks or beverages. Sugar is often considered synonymous with sucrose, and this creates the potential for confusion. We have continued to use the terminology chosen by the study authors, but it is important to note that most of the beverages in the United States are not actually sweetened with sucrose. The beverages may use a variety of caloric sweeteners, the most common of which is HFCS-55. In other countries, sucrose remains the primary sweetener used in beverages.

Literature Review of the Cross-Sectional Studies

Forshee and Storey (Forshee and Storey, 2003) found that BMI had a statistically significant and positive relationship with diet carbonated soft drink (DCSD) consumption for both boys ($p < 0.05$) and girls ($p < 0.05$). Since DCSD contain little, if any, energy, these beverages were most likely a marker, not a cause, of higher BMI values among study participants. Overweight children are more likely to consume DCSD in an attempt to control or decrease their weight. BMI did not show an association with regular carbonated soft drink (RCSD) or fruit drink/ade consumption.

A study by Forshee et al. (Forshee et al., 2004) found that the consumption of DCSD was positively associated with BMI for females using 24 hr data. Neither RCSD nor fruit drinks/ades were associated with BMI for females or males. In the FFQ, consumption of DCSD was also positively associated with BMI for females. No relationship was observed between any other beverage consumption category and BMI for either females or males.

French et al. (2003) analyzed soft drink consumption trends among children aged 6–17 years. These authors found that the overall prevalence of soft drink consumption among children aged 6–17 years was 48% higher in 1994–96, 98 than in 1977–78. Mean soft drink intake increased from 5 to 12 oz/day (155 to 370 g/day). The relationship between soft drink consumption and BMI was not examined.

Giammattei et al. (2003) investigated the relationship between BMI, television viewing, and regular and diet soft drink consumption among 305 non-diabetic sixth and seventh grade students from 3 different schools in Santa Barbara County, California. They discovered that 17.9% of the students were at-risk of overweight, while 17.4% of the students were overweight. Only the number of hours of television viewing on a school night and the total number of soft drinks consumed per day were significantly associated with BMI. When regular and diet soft drinks were analyzed separately, BMI z-scores and percent body fat remained positively and significantly associated with diet soft drink consumption only. BMI z-scores and percent body fat were not significantly associated with regular soft drink consumption.

Grant et al. (2004) studied the relationship between anthropometric status and macronutrient intake among Pacific Island children aged 2–5 years living in New Zealand. After adjusting for age and gender, the obese children consumed significantly more total energy than did the non-obese children. The obese children consumed more of all types of foods, not just more of specific foods, than did the non-obese children.

Nicklas et al. (2003) analyzed the relationship between BMI and food consumption patterns among 1562 African-American (AA) and Euro-American (EA) 10-year-olds. The authors found that EA males and EA females showed positive associations between overweight and consumption of sweets and sweetened beverages. For EA males and EA females, positive associations were also found between overweight and consumption of total foods and beverages, particularly from low-quality foods. AA females showed negative associations between overweight and consumption of fruits/fruit juices and fruit/fruit juices/vegetables, total number of meals consumed, and consumption of the breakfast meal. The total model explained about 4-8% of the variance in BMI for the various ethnic-gender groups, and soft drink consumption alone explained approximately 1% of the variance in the model.

Rajeshwari et al. (2005) assigned sweetened beverages to one of the following categories: soft drinks, fruit drinks, iced tea with sugar, and coffee with sugar. Study participants were categorized as non-consumers, low-consumers, medium-consumers, or high-consumers of sweetened-beverages. Between 1973 and 1994, mean BMI significantly increased for each of the four sweetened-beverage consumption categories. However, Rajeshwari et al. found no differences in mean BMI among any of the four consumption categories.

In their study of snacking trends among individuals aged 19–29 years, Zizza et al. (2001) found that sweetened beverages (regular soft drinks, diet soft drinks, and fruit drinks) were one of the major contributors of energy from snacking occasions. The relationship between snacking and BMI was not examined.

Summary of the Cross-Sectional Studies

The overall evidence for a positive association between consumption of soft drinks (HFCS proxy) and overweight and/or obesity is limited. Of the six cross-sectional studies that directly or indirectly investigated the relationship between soft drink consumption and prevalence of overweight and/or obesity, only Giammattei et al. and Nicklas et al. found a positive association. Two of the reviewed studies, French et al. and Zizza et al., did not include an analysis of the relationship between soft drink consumption and BMI.

In Giammattei et al., the association appears to be between the consumption of diet drinks and BMI. The reported association between regular soft drinks and BMI was not significant. Furthermore, Giammattei et al. found that only the sixth- and seventh-grade children who were consuming $\geq$3 soft drinks/day were more likely to have BMI values $\geq$85th percentile. This level of soft drink consumption is relatively large compared to the average soft drink consumption among children within this age group.

We conducted an original analysis to estimate the average consumption of soft drinks and the percentage consuming $\geq$3 soft drinks/day among the age group used in the Giammattei et al. study. We analyzed the most recent nationally representative data available—NHANES 1999–2002 (CDC, 2005)—and found that the mean combined consumption of regular fruit drinks/ades and RCSD for children aged 11–12 years is 450 g/day (95% CI = 397 to 503 g/day), or about 1.2 12-oz servings/day. We found that only those children above the 90th percentile consumed $\geq$3 soft drinks/day.

Nicklas et al. discovered that soft drink consumption explained approximately 1% of the variance in the model. The authors hypothesized that overweight status is not the result of a single eating pattern.

Four of the six studies do not support a relationship between consumption of a specific type of beverage (Forshee and Storey; Forshee et al.; Rajeshwari et al.) or a specific macronutrient (Grant et al.) and prevalence of overweight and obesity. Because sucrose and HFCS contain similar F:G ratios, the results from the Grant *et al.* study are relevant to the HFCS debate.

Literature Review of the Longitudinal Studies

The expert panel examined seven longitudinal studies that assessed the relationship between soft drinks—often utilized as a proxy for HFCS—and BMI of pre-schoolers, children, adolescents, and adult women.

Berkey et al. (2004) analyzed the relationship between BMI and intakes of sugar-added beverages, milk, fruit juices, and diet soda in a cohort of more than 10,000 males and females aged 9–14 years in 1996. These authors found a positive association between BMI and sugar-added beverage consumption for boys, but the association was not statistically significant for girls. When total energy was included in the model, the associations were not significant for either boys or girls.

In a cohort of 8203 girls and 6774 boys aged 9-14 years in 1996, Field et al. (Field et al., 2004) investigated the association between BMI and the intake of various snack foods, including sugar-sweetened beverages. No relationship was found between the snack food intake and the annual change in BMI for either girls or boys. According to these authors, "[w]hen servings per day of sugar-sweetened beverages were included as snack foods the association between snack food intake and change in BMI z-score was similar to the main findings" (Field et al., 2004).

Ludwig et al. (2001) examined the relationship between BMI and consumption of sugar-sweetened drinks among a cohort of 548 ethnically diverse schoolchildren aged 11–12 years enrolled in Massachusetts public schools. Over 19 months, the average sugar-sweetened drink consumption increased from 1.22 to 1.44 servings/day—a difference of 0.22 servings/day. There was a positive association between sugar-sweetened drinks and BMI with a magnitude of a 0.24 kg/m^2 increase in BMI for each additional serving/day increase in sugar-sweetened drink consumption. For the average increase in sugar-sweetened drink consumption (0.22 servings/day), this model predicted a BMI increase of 0.05 kg/m^2 assuming all other variables in the model remained constant. Nielsen and Popkin (2004) reported that between 1977 and 1996, the mean consumption of sweetened beverages increased from 2.02 to 2.55 servings/day for a mean increase of 0.53 servings/day. Using the Ludwig et al. estimate, the predicted increase in BMI would be 0.13 kg/m^2 for an increase of 0.53 servings/day of sugar-sweetened drink consumption.

Newby et al. (2004) explored the relationship between beverage consumption and changes in BMI in a cohort of 1345 children aged 2–5 years. These authors found no significant relationships between any of the beverages analyzed and BMI.

Schulze et al. (2004) examined the relationship between sugar-sweetened beverage consumption, weight change, and risk of type 2 diabetes among women aged 24–44 years at study initiation in 1989. More than half of the respondents were excluded from the Schulze et al. analysis because of various exclusion criteria. Those individuals with the greatest increase (≤ 1 drink/week to ≥ 1 drink/day) in their sugar-sweetened beverage consumption experienced a greater weight increase than other respondents. Those individuals with the greatest decrease (≥ 1 drink/day to ≤ 1 drink/week) experienced a smaller weight increase than other respondents. There was no difference in weight gain between those individuals who were consistently low consumers, consistently high consumers, or who made a smaller change in their consumption of sweetened beverages.

The low-high (≤ 1 drink/week to ≥ 1 drink/day) consumption category only contained about 2% of the study sample. About 75% of the study sample was located in the low-low (consistent at ≤ 1 drink/week) consumption category, and about 5% of the study sample was located in the high-high (consistent at ≥ 1 drink/day) consumption category. The results of the study suggest that those individuals in the high consumption category could benefit by reducing their consumption to ≤ 1 drink/week and that those individuals in the low consumption category could benefit by limiting their increase to no more than 2–6 drinks/week. Smaller changes in sweetened beverage consumption did not show any differences in weight gain.

Janket et al. (2003) examined the relationship between risk of type 2 diabetes and intakes of total caloric sweeteners, sucrose, fructose, glucose, and lactose among a cohort 38,480 female health professionals and found no association between the lowest versus highest consumption categories of total caloric sweeteners, sucrose, fructose, glucose, or lactose and risk of type 2 diabetes. Neither fructose nor glucose—the main components of HFCS—were related to the risk of developing type 2 diabetes. Sucrose, which has a F:G ratio very similar to that of HFCS, was also not related to the risk of developing type 2 diabetes.

Mrdjenovic and Levitsky (2003) examined the effects of excessive sweetened drink consumption [defined as >12 oz (>370 g)/day] on total energy intake and weight gain among 30 children aged 6–13 years attending the Cornell Summer Day Camp in 1997. They found that children who consumed >16 oz/day (>492 g/day) of sweetened drinks gained more weight than did children who consumed between 6 and 16 oz/day (186 and 492 g/day) of sweetened drinks, but none of these differences was statistically significant. The authors observed that "the sample size was too small (n = 21) to provide sufficient power for the observed difference in weight gain to be statistically significant" (2003). It is also possible that the observed difference in weight gain was not significant due to the absence of a relationship between sweetened drink consumption and weight gain.

Summary of the Longitudinal Studies

Of the four longitudinal studies examining growing children or adolescents, Berkey et al., Newby et al., and Mrdjenovic and Levitsky showed no association between BMI and the consumption of soft drinks. Only Ludwig et al. showed a significant increase of 0.24 BMI units over the previous 19 months for every additional serving increase in sugar-sweetened drink consumption. Berkey et al. estimated a non-significant increase of 0.019 and 0.015 BMI units from the previous year for each serving of sugar-added beverages consumed per day for girls and boys, respectively. Because of the large sample size in GUTS, this is a relatively precise estimate (95% CI = −0.008 to 0.046 for girls; 95% CI = −0.014 to 0.044 for boys, based on our calculations). We calculated the confidence intervals using Stata "p2ci" program which calculates a confidence interval based on the reported coefficient and p-value.

Janket et al. found no relationship between intakes of various caloric sweeteners and the risk of type 2 diabetes. Schulze et al. found that after four years, women who increased their consumption of sugar-sweetened beverages from ≤ 1/week to ≥ 1/day had higher BMI values by 0.47 kg/m^2 than did women who consistently consumed ≤ 1/week. Only 2% of the women in this study increased their sugar-sweetened beverage consumption from ≤ 1/week to ≥ 1/day, while 75% of the study participants consistently consumed ≤ 1/week. Overall, the mean BMI for the 96% of women who did not move from one extreme consumption category to another (low-high or high-low) was statistically indistinguishable regardless of the quantity of sweetened beverages consumed.

Field et al. did not report the estimated associations between sugar-sweetened beverage consumption and BMI.

Estimating the Relationship between Current RCSD Consumption Patterns and BMI

The potential impact of reducing RCSD consumption on BMI is a function of the strength of the association between the two and the amount of RCSD currently consumed. To assess this potential impact, we conducted an original analysis and applied current RCSD consumption patterns to estimates of the association between soft drink consumption and BMI from the longitudinal studies.

We obtained RCSD consumption data from NHANES 1999–2002 (CDC, 2005)—the most recent nationally representative survey available—for females and males aged 20+ years. These data show that the majority of survey participants consume only modest amounts of RCSD. We represented the full distribution of RCSD consumption via kernel density plots, which show the distribution of a variable by approximating the probability density function of consumption (Silverman, 1986). Similar to a

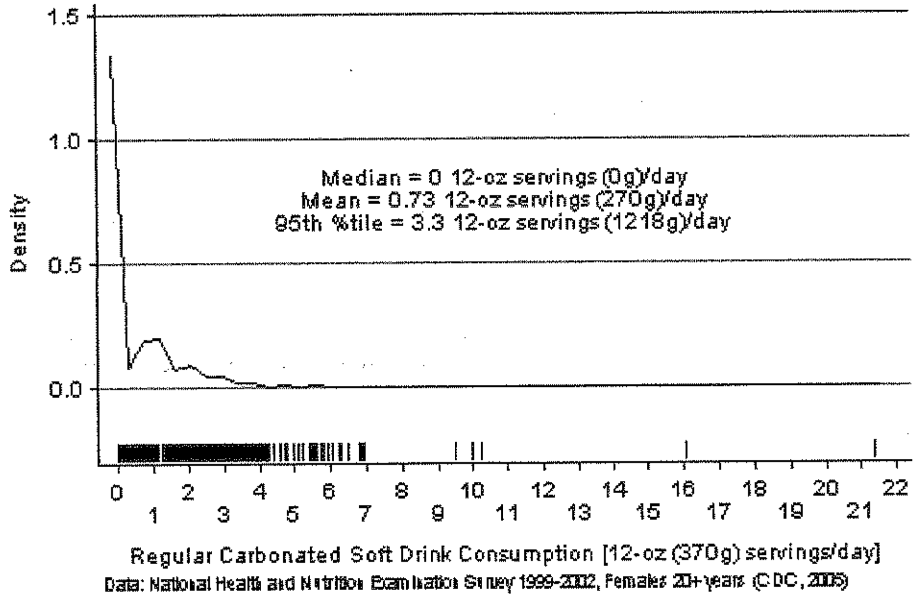

Figure 3 Kernel density distribution plot of regular carbonated soft drink (RCSD) consumption from NHANES 1999–2002 among females 20+ years. RCSD consumption is shown as the number of 12-oz servings consumed per day, and each 12-oz serving is equivalent to 370 g. The line graph represents the kernel density function for RCSD consumption. The kernel density function is an extension of the histogram and uses a "sliding window" to approximate the probability of consuming a given amount of RCSD across the entire distribution. Below the kernel density plot is a rug plot. Each vertical "pipe" in the rug plot represents a unique value for RCSD consumption. Rug plots are useful for visualizing extreme values in a data set. Figure produced by authors.

histogram, the height of the line is proportional to the percentage of respondents at any given level of consumption.

Kernel density plots of RCSD consumption for females and males show that the most commonly consumed amounts of RCSD are modest (Figs. 3 and 4). For both adult females and males, the most common amount is at 0 12-oz servings/day (0 g/day). Another, much smaller, peak is at 1 12-oz serving/day (370 g/day); a third, still smaller, peak is at 2 12-oz servings/day

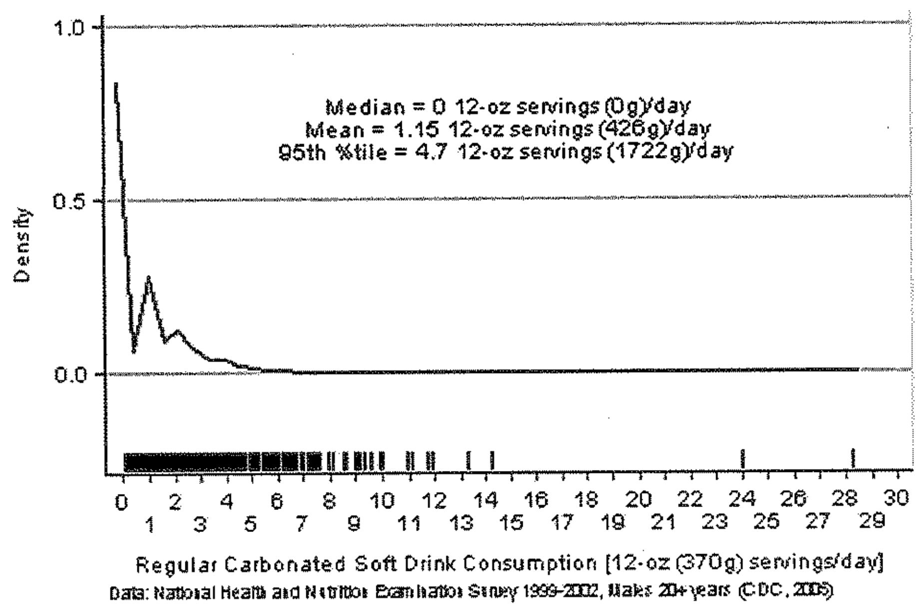

Figure 4 Kernel density distribution plot of regular carbonated soft drink (RCSD) consumption from NHANES 1999–2002 among males 20+ years. RCSD consumption is shown as the number of 12-oz servings consumed per day, and each 12-oz serving is equivalent to 370 g. The line graph represents the kernel density function for RCSD consumption. The kernel density function is an extension of the histogram and uses a "sliding window" to approximate the probability of consuming a given amount of RCSD across the entire distribution. Below the kernel density plot is a rug plot. Each vertical "pipe" in the rug plot represents a unique value for RCSD consumption. Rug plots are useful for visualizing extreme values in a data set. Figure produced by authors.

(740 g/day). The curve then asymptotically approaches zero with small upticks at whole numbers of servings. Beneath each kernel density plot is a rug plot to better visualize the extreme values in the data, particularly the handful of respondents with very high reported RCSD consumption levels. Each vertical line, or "pipe," represents a unique value for RCSD consumption. Above about 10 12-oz servings/day (3700 g/day) the rug plot becomes extremely sparse.

On the day of the 24HR, 59% of the females and 50% of the males aged 20+ years did not consume any RCSD. The mean consumption of RCSD was 0.73 12-oz servings/day (270 g/day) for females and 1.15 12-oz servings/day (426 g/day) for males. In the 95th percentile of RCSD consumption, females and males consumed 3.3 and 4.7 12-oz servings/day (1218 and 1722 g/day), respectively.

One limitation of NHANES 1999–2002 is that the dietary data are self-reported and may be subject to bias, particularly under-reporting. The upper percentiles of consumption observed in a 24 hr are generally known to be higher than the upper percentiles observed from either longer-term measurements of dietary intake or statistical estimates of usual intake (Tran et al., 2004; Nusser et al., 1993; Carriquiry et al., 1992).

Estimates of the relationship between soft drink consumption and BMI from longitudinal studies and our estimates of current RCSD consumption provide some parameters by which to approximate the impact that eliminating RCSD consumption would have on overweight and obesity rates in the United States. The estimates of the association between soft drink consumption and BMI in the longitudinal studies ranged from non-significant to a maximum of a 0.24 kg/m^2 change in BMI for each one serving/day change in soft drink consumption over 19 months. Using the Ludwig et al. (maximum) estimate, a female at the 95th percentile of soft drink consumption who eliminated soft drinks from her diet would reduce her BMI by about 0.825 kg/m^2. Using the Berkey et al. (non-significant) estimate—a 0.02 kg/m^2 change in BMI for each one serving/day change in soft drink consumption—the same female at the 95th percentile of soft drink consumption would reduce her BMI by only 0.066 kg/m^2.

A limitation of the discussion in this section is that it does not consider any possible long-term, cumulative changes in BMI as a result of changes in soft drink consumption. Extrapolating beyond the time frames used in the studies reviewed is difficult. Such extrapolation requires an assumption that the change increases proportionally with time. Rarely do we observe such simple proportional relationships over time. Changes often decelerate with time or even turn around completely. Therefore, in the absense of more direct evidence we can only offer vague speculation about what might happen over greater lengths of time and safely draw conclusions about what happens during the duration of our studies.

While it is impossible to rule out that weight change may continue beyond the time frames of the studies reviewed, the current models do not allow accurate projections beyond the original time frames.

RANDOMIZED CONTROLLED TRIALS

Overview

Randomized controlled trials (RCTs) are often considered the "gold standard" in research because they are not susceptible to confounding and are less susceptible to other forms of bias than are other types of studies (Coggon et al., 1997). We found only one RCT reported in the literature on the relationship between soft drinks and either BMI or weight gain.

Literature Review of the Randomized Controlled Trials

James et al. (James et al., 2004) performed a cluster RCT to study the effect of a focused educational intervention program on carbonated drink consumption and overweight and obesity in 644 children aged 7–11 years. Children in the intervention clusters participated in a program designed to emphasize the consumption of a balanced healthy diet and to discourage the consumption of both sweetened and unsweetened "fizzy" drinks (most likely sweetened with sucrose). James et al. observed a decrease in carbonated drink consumption of 0.6 glasses/3 days (50 ml/day) in the intervention group with an increase in carbonated drink consumption of 0.2 glasses/3 days (17 ml/day) in the control group. Mean percentage of overweight and obese children decreased by 0.2% in the intervention group and increased by 7.5% in the control group, and this difference was statistically significant. However, differences in average BMI values (0.1 kg/m^2; 95% CI = −0.1 kg/m^2 to 0.3 kg/m^2) and z-scores (0.04; 95% CI = −0.04 to 0.12) between the intervention and control groups were not statistically significant.

Summary of the Randomized Controlled Trials

There are no RCTs examining the direct relationship between HFCS consumption and overweight and obesity. The sweetened "fizzy" drinks studied by James et al. were almost certainly sweetened by sucrose, not HFCS, given that the study was conducted in Great Britain. Furthermore, James et al. did not show any difference in carbonated drink consumption and BMI between the treatment and control groups.

THEORIZED MECHANISMS

Overview

Three hypotheses have been proposed to support the argument that HFCS plays a unique role in weight gain compared with other caloric sweeteners. These hypotheses include:

1. HFCS increases the F:G ratio in the food supply, causing adverse metabolic effects that either directly or indirectly lead to weight gain.

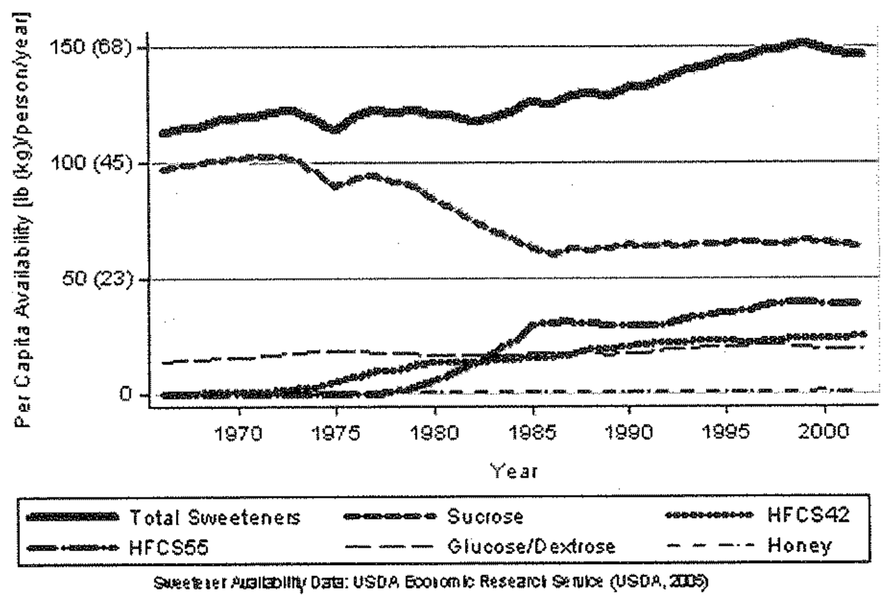

Figure 5 Per capita availability [lb (kg)/person/year] of total sweeteners, sucrose, HFCS-42, HFCS-55, glucose (dextrose), and honey in the U.S. food supply from 1966 to 2002. The various line graphs represent the per capita availability of the different types of sweeteners in the U.S. food supply based on USDA ERS food availability data. Figure produced by authors.

2. HFCS is "sweeter" than sucrose, leading to over-consumption of foods containing HFCS and weight gain.
3. Consumption of beverages, which are almost exclusively sweetened with HFCS, does not stimulate satiety signals, leading to over-consumption and weight gain.

HFCS Increases the F:G Ratio in the Food Supply

The term "high fructose corn syrup" has generated some confusion. HFCS is high in fructose compared to the original dextrose-based corn syrups, which contain no fructose. HFCS is compositionally similar to sucrose, which contains a F:G ratio of 50:50.

The confusion over the meaning of "high fructose" has led some researchers to speculate that the introduction of HFCS has increased the F:G ratio in the U.S. food supply. Fructose metabolism studies show that fructose absorption from the gut is dependent on the presence of glucose (Riby et al., 1993; Ravich et al., 1983). Unabsorbed fructose is either fermented in the colon or excreted in the feces. However, some researchers propose that an increase in free fructose in the food supply has contributed to adverse metabolic changes that have led to increased overweight and obesity rates.

To address this question, we conducted original research to calculate the changes in total glucose and fructose availability and the F:G ratio in the food supply since the introduction of HFCS-42 in 1966. There are serious limitations to the USDA Economic Research Service (ERS) food availability data, particularly if one needs to make inferences about associations at the individual level. Our purpose here is only to assess the trends in fructose and glucose availability and their ratio. This provides more information than is currently available about the impact that the introduction of HFCS has had on the relative amount of fructose and glucose in the food supply. This analysis is subject to the same limitations discussed earlier regarding ecological data. Ideally, the analysis should be conducted at the individual level by examining the associations between fructose and glucose consumption and BMI. Unfortunately, such data are not currently available.

Many caloric sweeteners in the food supply contain various formulations of fructose and glucose. Data for per capita sweetener availability (Fig. 5) were obtained from the USDA ERS disappearance series (USDA, 2005). Using the percentage of fructose and glucose for each of the major sweeteners, we calculated the total fructose and total glucose available from caloric sweeteners in the U.S. food supply (Fig. 6). Data for the fructose and glucose composition of sweeteners were obtained from Hanover and White (Hanover and White, 1993). The data in Fig. 6 do not include the glucose that is available from other carbohydrate sources (e.g. starches, maltodextrins, etc.) or the fructose that is naturally available in certain fruits and vegetables.

Until the mid-1960s, sucrose was the primary sweetener in the American diet. A 1993 study by Park and Yetley (1993) noted that HFCS had replaced sucrose in many foods and beverages. These scientists remarked that "from the standpoint of fructose metabolism the source of fructose, whether free or from sucrose, is not important because bound fructose is readily liberated in the food product and in the small intestine. The total fructose in the diet is the most important consideration." (Park and Yetley, 1993) Although the type of sweetener used in the U.S. food supply has changed over the last few decades, the total amount of

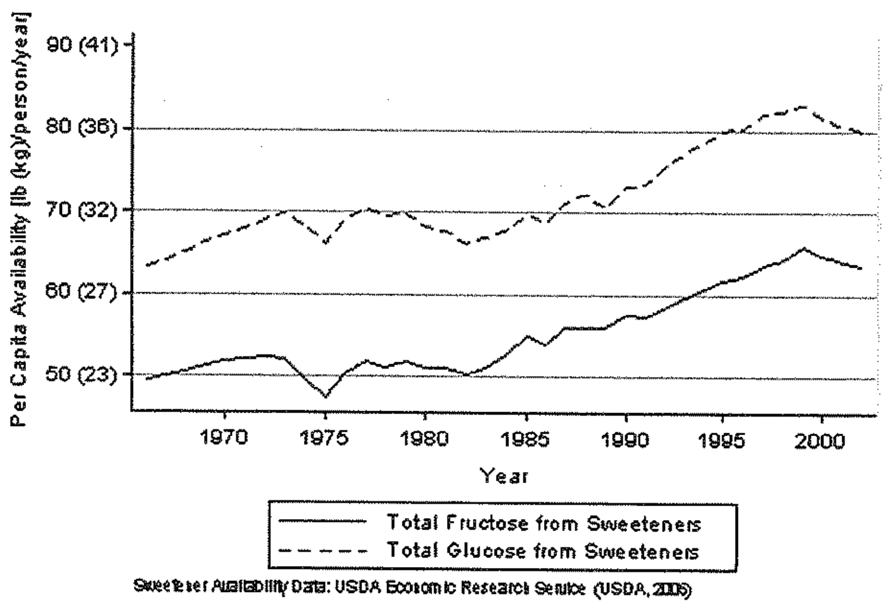

Figure 6 Per capita availability [lb (kg)/person/year] of total fructose and total glucose from caloric sweeteners in the U.S. food supply from 1966 to 2002. The solid line graph represents the per capita availability of total fructose from all sweetener sources, and the dashed line graph represents the per capita availability of total glucose from all sweetener sources. Both graphs are based on USDA ERS food availability data. Sweetener availability calculations do not include glucose available from other carbohydrate sources (e.g. starches, maltodextrins, etc.) or fructose naturally available in certain fruits and vegetables. Figure produced by authors.

fructose (free and bound) from sweeteners has remained relatively constant according to Park and Yetley. Since the F:G ratio of sucrose and HFCS are nearly identical, replacing the free and bound fructose from sucrose with the free fructose from HFCS had virtually no effect on the availability of the total amount of fructose from sweeteners. In the decade since the Park and Yetley paper was published, however, soft drink (RCSD and fruit drinks/ades) consumption has increased.

Data from the USDA ERS show that sweetened beverage consumption increased between the late 1970s and mid-1990s. In addition, Yen and Lin (2002) reported that the percentage of children and adolescents who drink carbonated soft drinks rose from 44% in the 1970s to 49% in the 1990s. Average consumption increased for children aged 6–11y and adolescents aged 12–17y.

There have been significant changes in the total availability of caloric sweeteners in the U.S. food supply. From 1966 to 1999, the total per capita sweetener availability increased, despite some temporary declines in the 1970s and 1980s. Since 1999, however, the total per capita sweetener availability has declined by 5 lb (2.3 kg)/person/year. The mix of sweeteners has also changed. Sucrose availability fell substantially during the 1970s and early 1980s before stabilizing in the mid–1980s. HFCS-42 began to be incorporated into the food supply around 1970 and has since steadily increased. HFCS-55 began to be utilized in the mid-1970s, increased rapidly in the early 1980s, and continued to gradually increase until 1999.

We conducted a new analysis of the USDA ERS food availability data to examine the ratio of fructose to glucose since 1966. Throughout this time period, the availability of glucose was more than 10 lb (4.5 kg)/person/year higher than the availability of fructose, and the trends in total fructose and total glucose are very similar (Fig. 7). For each year, the total available fructose was divided by the total available glucose to create a ratio. For reference, we included a line at 1.0 to indicate what the ratio would be if only sucrose were used in the food supply. The F:G ratio has been substantially less than 1.0, and has stayed in a narrow range between 0.71 and 0.80. From 1966–1975, the F:G ratio actually fell as HFCS-42 (42:53 ratio) was replacing sucrose (50:50 ratio) in some foods. With the introduction of HFCS-55 (55:42 ratio), the F:G ratio began returning to its previous level before the introduction of any HFCS product. In 2002, the F:G ratio was 0.79 compared to 0.78 in 1966.

These trends contradict the hypothesis that the introduction of HFCS increased the F:G ratio in the U.S. food supply. Moreover, most RCT studies of fructose consumption have used F:G ratios well above 1.0. For example, in Swanson et al. (1992) subjects in the fructose treatment consumed 100 g of fructose, 10 g of sucrose, and 23 g of "other" carbohydrates. Even if all 23 g of "other" carbohydrates are assumed to be glucose, the F:G ratio for these subjects would be 3.75, which is more than 4 times the largest F:G ratio typically observed in the food supply.

HFCS is "Sweeter" than Sucrose

The monosaccharides—fructose, glucose, and galactose—and the disaccharides—lactose, sucrose, maltose, and trehalose—have varying degrees of sweetness. Of the monosaccharides, crystalline fructose imparts the "sweetest" taste with

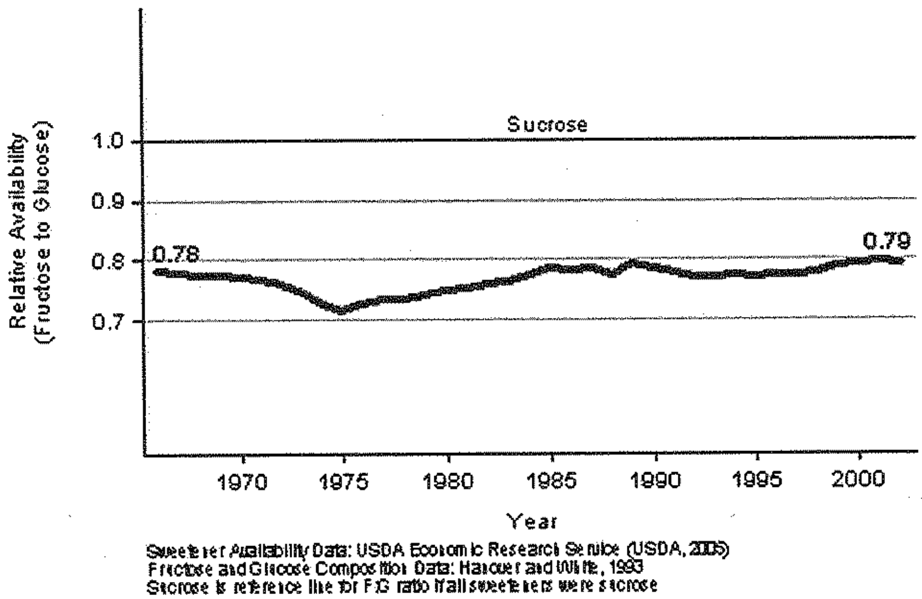

Figure 7 Relative availability of fructose:glucose (F:G) in the U.S. food supply from 1966 to 2002. The line graph represents the ratio of per capita availability of fructose from all sweetener sources and per capita availability of glucose from all sweetener sources based on USDA ERS data. The straight line at 1.0 represents the theoretical F:G ratio if sucrose were the only sweetener available in the food supply. Figure produced by authors.

a relative sweetness of 173 compared with crystalline sucrose, which has been designated as the reference and set at 100. Glucose, galactose, and lactose are less sweet than sucrose with relative sweetness scores of 74, 33, and 16, respectively (Biology, 2004).

Bray et al. (2004) hypothesized that HFCS-55 is much "sweeter" than sucrose. They conjectured that a corresponding increase in the sweetness of the food supply created cravings that induced people to over-consume sweetened beverages, leading to a positive energy balance and weight gain. Unfortunately, the authors miscalculated the relative sweetness of HFCS-55 by using the sweetness value of crystalline fructose rather than aqueous fructose. Expert sensory panels have confirmed that an aqueous solution of fructose at 10% dry solids and room temperature has a relative sweetness of 117 (Hanover and White, 1993). Calculating the relative sweetness of HFCS-55 using the sweetness value of aqueous fructose yields a sweetness value almost identical to the aqueous sucrose standard. Moreover, a recent study concluded that temperature had little effect on sweetness intensity (Schiffman et al., 2000). Therefore, the hypothesis that HFCS-55 is "sweeter" than sucrose and creates cravings that induce over-consumption and weight gain seems implausible.

Beverages, a Major Source of HFCS, do Not Stimulate Satiety Signals

Although the underlying factors contributing to weight gain are multiple and complex, it is widely acknowledged that weight gain generally occurs because of a long-term imbalance between energy consumed and energy expended. Some scientists hypothesize that overweight and obesity rates have dramatically increased for both children and adults because soft drink consumption (HFCS proxy) has increased since the 1970s. Although weight gain can be linked to various patterns of over-consumption, liquid calories are thought by some researchers to be less satiating than calories obtained via consumption of solid foods. The lack of satiety produced by soft drinks then leads to over-consumption and weight gain.

Several mechanisms may account for liquid calories being less satiating. The mastication of solid foods may stimulate a satiety signal that is not activated when liquids are consumed. Initial pancreatic exocrine and endocrine responses to oral stimulation are greater for non-liquids than they are for liquids; initial pancreatic responses that include insulin release may modulate postprandial metabolism. This includes glucose tolerance with possible hunger and eating effects (DiMeglio and Mattes, 2000).

Satiation refers to the reduction in the amount of energy consumed at a particular meal, whereas satiety refers to the reduction in the amount of energy consumed at a subsequent meal or meals (Almiron-Roig et al., 2003). The total volume of a solid or liquid appears to contribute to satiety; that is, consumption of a large volume of foods or beverages at a particular meal or eating occasion (snack) reduces the amount of energy consumed at future meals or eating occasions.

Studies conducted by Rolls and colleagues show that high-volume/less-energy-dense liquids, such as soups, vegetable juices, and milk, are satiating because of their high water content (Bell et al., 2003; Rolls et al., 1999; Rolls et al., 1990). Other researchers contend that solid foods are more satiating (DiMeglio and Mattes, 2000).

An RCT with 24 women aged 20–37 years with a mean BMI of 22.6 kg/m^2 examined the effects of three isoenergetic

(1128 kJ) preloads on satiety and subsequent food intake (Rolls et al., 1999). Participants consumed breakfast, lunch, and dinner at the study site on four separate test days with at least one week separating each test. Three of the test days included the consumption of a preload prior to the lunch meal, while no preload was consumed on the remaining test day (control). The three preloads included chicken and rice casserole, chicken and rice casserole with a glass of water, and chicken and rice soup.

Mean energy consumed during the control lunch meal (no preload) was significantly greater (2693 $\pm$ 166 kJ) than mean energy consumed during the lunch meals preceded by either the casserole (1639 $\pm$ 148 kJ; $p < 0.05$), the casserole with water (1657 $\pm$ 148 kJ; $p < 0.05$), or the soup (1209 $\pm$ 125 kJ; $p < 0.05$) preloads. In addition, after adding the energy obtained from the preload to the energy consumed during the subsequent lunch meal, Rolls et al. found that the women consumed significantly less energy (16%) with the soup preload than with either the casserole or the casserole with water preloads. Since energy intakes during the dinner meal were similar regardless of the preceding lunch condition, the women did not compensate for the reduced energy intake from the lunch meal with the soup preload.

DiMeglio and Mattes (2000) conducted a study examining the effects of supplementing the diets of 15 free-living individuals with 450 kcal/day from either jelly beans (solid load) or carbonated soft drinks (liquid load). The duration of each treatment was four weeks with a four-week washout period between treatments. For each four-week treatment period, the participants were instructed to increase their total consumption by ingesting the required amount of jelly beans [approximately 4 oz (113 g)/day] or carbonated soft drinks [approximately 3.2 12-oz servings (1184 g)/day]. Twenty-four hour dietary recalls of food consumption were randomly conducted six times during the four-week treatment periods. The study included one hunger rating experiment lasting 180 minutes.

Although participants were instructed to increase their caloric consumption by 450 kcal/day over each four-week treatment period (12,600 kcal total), physical activity did not increase significantly. The study reported a 118% compensation for the solid load, but a -17% compensation for the liquid load. However, there was no significant difference in hunger ratings. Mean body weight increased by 0.3 kg and 0.5 kg during the jelly bean and carbonated soft drink treatment periods, respectively. Mean BMI increased by 0.1 kg/m^2 during both treatment periods. Although the mean body weight and BMI increased after each treatment period, the increases were significant only for the liquid treatment period ($P \leq 0.05$ for both). However, the change in mean body weight and BMI was not statistically significant between the two treatments.

More rigorous research focused on the satiety and satiation differences of liquids versus solids is needed. Controlled, metabolic feeding studies are also needed to refute or confirm epidemiologic studies and to examine possible differences in absorption, metabolism, and utilization of HFCS versus sucrose. Additional RCTs examining associations between weight gain and consumption of sweetened beverages, various sweeteners, and total energy, as well as studies designed to increase the understanding of food intake behaviors, are needed. These RCTs should include analyses of individual differences in blood lipids, glucose tolerance, and certain hormones and peptides (i.e. insulin, ghrelin, leptin, glucagon-like peptide, etc.) in response to the consumption of various sweeteners. Currently, there are no studies that directly compare biological responses of HFCS versus sucrose consumption.

RESEARCH GAPS

The expert panel identified several research gaps. No studies examined whether HFCS is metabolized differently than sucrose. This is a critical research gap and should receive the highest priority for future research on this question. While it appears likely that the biological effects of HFCS and sucrose are similar, it is premature to conclude whether or not there are any differences in the mechanisms by which sucrose and HFCS are metabolized in the absence of this important research. The results from fructose studies can not be extrapolated to HFCS because the typical F:G ratio found in these fructose studies is much higher than the F:G ratio found in HFCS.

Updating the USDA food composition and nutrient databases for key food groups should be the second priority. HFCS levels in most food products have not been quantified, and no information concerning individual-level consumption of HFCS is currently available. This is an important data need that prevents crucial epidemiological research. Fructose levels in food products and actual fructose consumption are also largely unknown. Without data on the HFCS and fructose concentrations of foods, it is impossible to identify the high consumers of fructose and develop epidemiologic models of their relative risk for overweight and obesity or other health endpoints. Furthermore, no analytical chemistry methods exist to distinguish naturally-occurring dietary fructose from the fructose added by manufacturers either as sucrose or HFCS.

One specific research need is a more detailed investigation of the vulnerabilities of sub-populations. Some sub-populations may be particularly susceptible to overweight and obesity due to the over-consumption of caloric sweeteners, but there are no studies addressing this possibility. Individuals with strong family histories of overweight and obesity and/or those who are entering life stages that are associated with weight gain need particular attention.

Some more general research gaps should also be addressed. Increased access to federally-funded longitudinal datasets is needed in order to replicate the findings of other researchers.

Additional studies are needed to better measure energy expenditure and its relative importance to weight control and prevention of weight gain.

OVERALL STRENGTH OF THE EVIDENCE

The evidence that HFCS consumption uniquely increases the risk of weight gain is very weak. Few studies directly explore the relationship between HFCS, body weight, and BMI. The only evidence directly linking HFCS consumption and weight gain is ecological data. Ecological data are widely recognized as insufficient for establishing cause-effect relationships.

The prospective observational studies typically utilized soft drinks as a proxy for HFCS. Three of the four studies of youth reviewed in this manuscript found no association between soft drinks and BMI while the third found a significant association of 0.24 kg/m^2 for each one serving/day change in consumption.

Cited mechanisms proposing a positive relationship between HFCS consumption and weight gain have major gaps. The hypothesis that the increasing levels of HFCS in the food supply has increased the F:G ratio is not supported by the USDA ERS food availability data. The F:G ratio actually fell after the introduction of HFCS-42, rose slightly after the introduction of HFCS-55, and is now currently only .01 higher than it was before the introduction of HFCS-42. The claim that HFCS is "sweeter" than sucrose is not supported by expert sensory panels. This claim appears to be the result of incorrectly calculating the relative sweetness of HFCS-55 based on the relative sweetness value of crystalline fructose instead of the relative sweetness value of fructose in solution.

CONCLUSIONS

The impact of HFCS consumption on BMI must be put in context with other broad economic and societal changes during the past several decades. Many other plausible explanations for rising overweight and obesity rates exist, including a decrease in smoking (Janzon et al., 2004; Rodu et al., 2004; Koh-Banerjee et al., 2003); an increase in sedentary occupations (Lakdawalla and Philipson, 2002); an increase in two-income households and single-parent households (Anderson et al., 2003; Crepinsek and Burstein, 2004); transportation and infrastructure changes that discourage physical activity (Bell et al., 2002; Lanningham-Foster et al., 2003); a decrease in PE classes and extracurricular sports programs in schools (Andersen et al., 1998); an increase in sedentary forms of entertainment (i.e. TV/movie viewing, video games, etc.) (Sternfeld et al., 2004); demographic changes (i.e. aging population, immigration, etc.) (Hedley et al., 2004; USD-C, 2002; Guzman 2001); a decrease in food costs with increase in food availability (Lakdawalla and Philipson, 2002); and changes in food consumption patterns (Diliberti et al., 2004; Binkley et al., 2000).

The expert panel concluded that the currently available evidence is insufficient to implicate HFCS per se as a causal factor in the overweight and obesity problem in the United States. However, there are significant knowledge gaps and weaknesses in existing research, so further research is warranted. Nevertheless, in a society that is experiencing unhealthy weight gain, it is necessary for many individuals to reduce their energy intake, including, but not limited to, energy provided from calorie-dense foods and beverages. Many individuals also need to increase their level of physical activity to help achieve and maintain a healthy weight and to reap the other health benefits of physical activity (USDA, 2005).

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Lack of findings for the association between obesity risk and usual sugar-sweetened beverage consumption in adults – A primary analysis of databases of CSFII-1989–1991, CSFII-1994–1998, NHANES III, and combined NHANES 1999–2002

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Abstract

The relationship between obesity risk and sugar-sweetened beverage (SSB) consumption was examined together with multiple lifestyle factors. Statistical analysis was performed using population dietary survey databases of USDA CSFII 1989–1991, CSFII 1994–1996, CDC NHANES III, and combined NHANES 1999–2002. Totally, 38,409 individuals, ages 20–74 years, with accompanying data of dietary intake, lifestyle factors, and anthropometrics were included in the descriptive statistics and risk analysis. Analytical results indicate that obesity risk was significantly and positively associated with gender, age, daily TV/screen watching hours and dietary fat content, and negatively associated with smoking habit, education and physical activity; obesity risk was not significantly associated with SSB consumption pattern, dietary saturated fat content and total calorie intake. No elevated BMI values or increased obesity rates were observed in populations frequently consuming SSB compared to populations infrequently consuming SSB. Additionally, one-day food consumption data was found to overestimate SSB usual intake by up to 38.9% compared to the data of multiple survey days. *Conclusion:* multiple lifestyle factors and higher dietary fat intake were significantly associated with obesity risk. Populations who frequently consumed SSB, primarily HFCS sweetened beverages, did not have a higher obesity rate or increased obesity risk than that of populations which consumed SSB infrequently.

Keywords: Sugar; Beverage; Obesity; HFCS; Risk; Database

1. Introduction

The prevalence of obesity is increasingly recognized as a global health problem, and the WHO MONICA Project has associated the increasing dietary energy supply with the increase in personal weight in Western countries (Silventoinen et al., 2004). Several mechanisms on obesity prevalence have been proposed, but one obvious underlying mechanism is a positive balance between energy intake and energy expenditure. The consequence from excessive weight gain and obesity, defined by body mass index (BMI) equal to or over 30, is the increased risk of various diseases, including cardiovascular disease and diabetes. Obesity lowers quality of life, decreases productivity, and results in billions of dollars in associated health care costs. Currently, there are few indications that the increasing

Abbreviations: HFCS, high fructose corn syrup; SSB, sugar-sweetened beverage; CSFII, continuing surveys of food intakes by individuals; NHANES, national health and nutrition examination surveys; BMI, body mass index.

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prevalence of obesity has reached its plateau in the US (Blanck, 2006). Recent publications and commentaries have suggested that the consumption of added sugars from sucrose, high fructose corn syrup (HFCS), or sugar-sweetened beverage (SSB) is a direct causative factor for the development of obesity (Bray, 2004; Bray et al., 2004; Nielsen and Popkin, 2004). Although some reports draw simple correlations between obesity and SSB consumption using population trends and national food production data, these approaches do not take into account the actual consumption and event occurrence by individuals, nor do they account for many other physical/medical aspects linked with the event occurrence. Simple correlations must be examined carefully when used to predict direct causality of a non-communicable medical condition by using other criteria (Hill, 1965), such as prospective intervention studies. Other reports have provided a more direct analysis on causality of food intakes and body weight status by examining data or databases which contain individual records of food consumption and anthropometrics (Janket et al., 2003; Kvaavik et al., 2005; Schulze et al., 2004; Wu et al., 2004; Yang et al., 2003).

During the last 30 years, high fructose corn syrup has gradually replaced cane and beet sugar sucrose in most US beverage applications. HFCS, like sucrose, is compositionally made up of approximately equimolar amounts of fructose and glucose. HFCS typically comes in either 42% or 55% fructose content, with the remainder being mainly glucose. In sucrose, the two monosaccharides, fructose and glucose, are chemically bonded together while in HFCS, the glucose and fructose are a simple mixture. During ingestion and absorption, sucrose is hydrolyzed into fructose and glucose by stomach acid and cleaving enzymes in the digestive tract, so that sucrose does not actually appear in the bloodstream (Gray and Ingelfinger, 1966). Furthermore, the mixture of glucose and fructose act differently than a pure monosaccharide ingested singly (Riby et al., 1993). Nutritionally and metabolically, it is unlikely that the human body can distinguish whether the two monosaccharides come from sucrose or HFCS once absorbed into the bloodstream. It is also interesting to note that even when sucrose is used in soft drinks, as in Europe and Mexico, the sucrose is often more than 50% hydrolyzed into fructose and glucose, which helps to maintain a constant sweetness level during storage and also due to the fact that sucrose inverts (hydrolyzes) spontaneously in acidic beverage conditions (Birkhed, 1984; Marov and Dowlong, 1990; Riby et al., 1993).

Very limited long term prospective data are available to examine the association between HFCS and obesity. In general, it is very difficult and expensive to conduct a prospective population study to determine the effect of a single dietary component on obesity occurrence. In this study, we have used the approaches of descriptive statistics and Logistic regressions using multiple dietary intake survey databases to investigate the potential influence of multiple lifestyle factors and sugar-sweetened beverage (SSB) consumption on BMI profiles and obesity occurrence rates in the US adult population. To our knowledge, this is the first work using the five population databases nationally surveyed during 1988–2002 to examine a correlation between obesity, certain lifestyle factors, and SSB consumption.

2. Methods

2.1. Databases and subjects

US food intake data were analyzed from the two USDA Continuing Surveys of Food Intakes by Individuals (CSFII) 1989–1991 and 1994–1996, and the three CDC National Health and Nutrition Examination Surveys (NHANES) III 1988–1994, NHANES 1999–2000, and NHANES 2001–2002 (National Center for Health Statistics of CDC; The Food Surveys Research Group, 1989–1991; The Food Surveys Research Group, 1994–1996). From these five food intake databases, 38,409 adults, who had complete data records required for this analysis, were included in this study. Relationships were examined between lifestyle factors/SSB consumption and BMI/obesity occurrence. Data records were selected for analysis from adult population aged 20–74 years, as this population is more stable and not as subject to lifestyle or development changes radically affecting height and weight over short periods of time. Additionally, children and adolescents lack certain lifestyle data such as smoking habit, education level, etc., which would bias the risk analysis. Elderly adults are also subject to more health-related issues that may affect body weight and lifestyle patterns. In view of the relatively smaller sample sizes, we followed the recommendations from the analysis guide for NHANES data, and merged the databases of NHANES 1999–2000 and NHANES 2001–2002 together as "NHANES 1999–2002".

2.2. Term definition and data categorization

Among these databases, some inconsistencies of criteria for data collection exist. First, the number of days of survey periods was not always the same. NHANES databases only have one-day (24 h) food intake data, whereas CSFII 1994–1996 database has two-day and CSFII 1989–1991 database has three-day food intake data. Secondly, methods for collecting data on physical activity are different. In order to generate consistency, we categorized physical activity for each individual as active/vigorous, moderate, and minimal for each database, similar to the classification in NHANES 1999–2002. Thirdly, for TV/screen watching time, some databases include computer time, others do not, and NHANES III did not collect the data of TV watching time in the adult population. In this study, TV/screen time is divided into three levels: less than 2 h, 2–4 h, and more than 4 h. Fourthly, for education records, CSFII databases use highest school year attained, while NHANES 1999–2002 databases use categories (under high school, high school diploma, or more than high school). We used the latter for categorization of education level for all databases. Smoker was defined as a person who currently smokes cigarettes, cigars, and/or pipes. To analyze age effects, specific age groups were segmented into either 5 or 10-year intervals. Lastly, as defined by the CDC, obesity is characterized as an adult with a BMI $\geqslant 30$.

Sugar-sweetened beverages (SSB) were defined as caloric soft drinks, colas, and sugar sweetened fruit beverages. Typically, these are predominately sweetened with HFCS in the US. Pure fruit juices and diet soft drinks were not included in this category. In total, 73 SSB products that met the SSB definition were found in the databases. The frequent consumers, or "users", of SSB were defined as those individuals who consumed any kind of SSB at least once during the defined survey period. Otherwise, individuals were categorized as infrequent SSB consumers, or "non-users".

2.3. Statistical method

SAS software (version 9.1, SAS Institute, Cary, NC) was employed as the statistical evaluation tool. Descriptive statistics on obesity rates, SSB intake amounts, sugars from SSB, daily energy, % fat calories, % saturated fat calories, BMI, and incidence of obesity were performed with adjustments for population sample weights. Because of the dissimilarities of survey length/days among the databases, we also examined how this impacted the estimation of mean intakes for sugar sweetened beverage amounts using CSFII data, which have the data collected from multiple days. The intake means between whole survey period (averages of 2 or 3 days) and only consuming day(s) of CSFII data were determined and then related to the 1 day data of NHANES surveys. As previously reported, food and nutrient intake data in the population are usually not normally distributed, potentially leading to inaccurate estimates of the usual intake in the population (Nusser et al., 1996). We examined the data distribution of SSB intakes and found the data to be right skewed. Thus, the SSB intake data were power-transformed to an approximate normal distribution, and the intake means were further calculated (Carriquiry, 2003; Freedman et al., 2004; Hoffmann et al., 2002; Nusser et al., 1996). For the purpose of comparison, both means obtained from original data and transformed data were reported.

Logistic regression (Logit) procedures were used to conduct the risk analysis in the adult population (age 20–74). For the risk analysis, obesity status (yes or no) was used as the dependent variable in the analysis models. Independent (explanatory) variables included SSB use, gender, age group, current smoker, education levels, TV watching hours, physical activity level, fat intake level, saturated fat intake level, and daily energy intake level. Subjects who lacked these data were not included in the risk analysis.

3. Results

3.1. Obesity prevalence

Numerous statistical analyses of population data for obesity prevalence in the US have been reported (Centers for Disease Control and Prevention; Morrill and Chinn, 2004). However, due to dissimilarities in population samples, methods of data collection, sampling deviation, and statistical methods, reported occurrence rates of obesity are often not identical even for the same time period. In this study, we calculated obesity occurrence by age groups over the adult population with age range of 20–74 years old. Table 1 lists the obesity occurrence percentages in the defined adult population by gender, lifestyle factors, SSB frequent/infrequent user, percent of fat calories, percent of saturated fat calories, and energy intake levels. The data indicate that: (1) obesity rates are increasing overtime and women have a faster and higher upsurge; (2) tobacco smokers have a lower obesity percentage; (3) a higher physical activity level and a higher education level

Table 1
Obesity occurrence by lifestyle and dietary factors in adults (age 20–74)

Factors	Categories	% Obesity occurrence (weighted data)			
		CSFII 1989–1991, $n = 8974$	CSFII 1994–1996, $n = 8507$	NHANES III 1988–1994, $n = 13741$	NHANES 1999–2002, $n = 7187$
Gender	Men	14.48	17.51	19.80	27.50
	Women	14.89	19.27	25.04	34.41
Smoking	Yes	12.95	16.80	18.23	25.58
	No	15.33	18.96	24.50	32.99
Education	<High school	19.90	24.96	27.62	33.95
	High school	15.96	20.90	25.08	33.73
	>High school	11.99	15.00	17.75	28.51
TV/screen hours	<2	10.12	15.09	No data	23.45
	2–4	14.40	21.30	No data	30.73
	>4	19.54	24.89	No data	40.82
Physical activity	Active	7.55	15.78	16.70	18.78
	Moderate	12.56	14.72	18.97	30.35
	Minimal	19.82	23.13	28.61	37.28
SSB user	Frequent	15.17	18.30	20.05	30.35
	Infrequent	14.22	18.52	24.53	31.60
% Fat calories	<30	10.61	15.98	19.55	26.59
	30–39	14.28	20.73	24.00	33.04
	⩾40	18.60	23.13	25.89	37.14
% Satu-fat calories[a]	<10	12.76	15.90	19.85	28.06
	10–<15	16.43	19.27	23.23	32.35
	⩾15	16.63	23.05	25.68	35.80
Calories/day	<1000	17.16	22.50	28.24	37.87
	1000–<1500	14.06	19.50	23.98	32.32
	1500–<2000	14.85	18.80	23.91	30.40
	2000–<2500	13.79	15.27	22.67	30.35
	2500–<3000	12.94	19.08	22.50	29.10
	3000–<3500	16.99	16.59	15.55	35.52
	3500+	17.44	18.64	18.00	25.13

[a] Satu-fat = saturated fat.

are associated with lower obesity percentages; (4) longer TV/screen watching time is linked to higher obesity percentages; (5) SSB frequent users had similar obesity percentages compared to infrequent users; (6) a higher dietary fat or saturated fat content correlates with a higher obesity percentage; and (7) the higher daily energy intake levels appeared to be not related to an increased obesity occurrence trend.

Mean BMI values and obesity occurrences between SSB frequent and infrequent users by age group were compared. Sample individuals were grouped by 5-year age interval. Fig. 1a–d shows obesity occurrence percentages by age group for the 4 data sets, while Fig. 2a–d shows the BMI data for the same population and age groups. The obesity occurrence rates from all databases except NHANES 1999–2002 show a similar increase in obesity until around

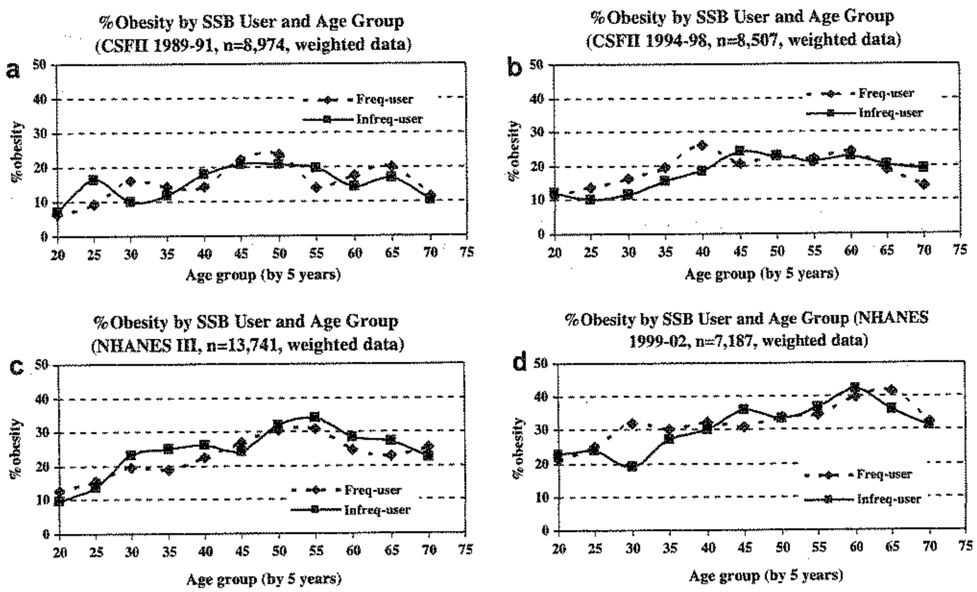

Fig. 1. Obesity occurrence rates by SSB frequent (freq-)/infrequent (infreq-) users and age groups.

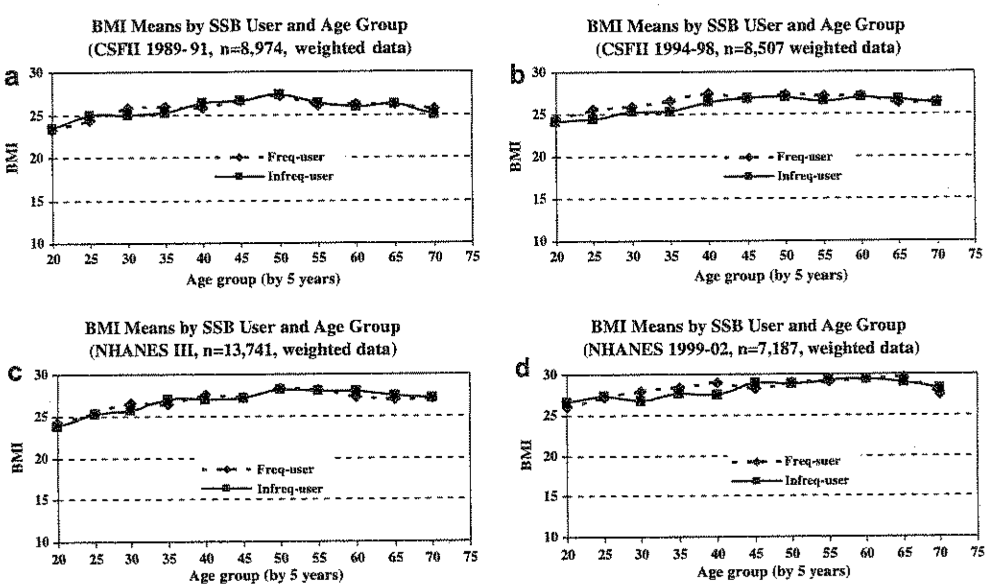

Fig. 2. Mean BMI by SSB frequent (freq-)/infrequent (infreq-) users and age groups.

age 50 years, followed by a decline. Percentages of obesity from NHANES 1999–2002 data (Fig. 1d) extended this maximum plateau to around 60 years old, and the respective values being clearly increased compared to the other survey data (Fig. 1a, b, or c vs d) for corresponding age groups. However, the curves of obesity percentages are intertwined between SSB frequent and infrequent users. Meanwhile, curves of mean BMI between SSB frequent and infrequent users are much smoother and are basically overlapping (Fig. 2a–d). These data suggest sampling error may be a major reason for the intertwining of obesity curves. This arises because the sample n became smaller after grouping subjects into each age group (by a 5-year interval). The fluctuations of the obesity curves between SSB frequent and infrequent users did not show a clear pattern among the databases. For example, the obesity rates in a certain age group in the frequent users were neither always higher nor lower than the values in infrequent users for all databases. Thus, it is less likely that SSB consumption pattern had a predictable impact in a specific age group. For either obesity rates or BMI changes with age, the shapes and magnitudes of the curves between SSB frequent and infrequent users are essentially not different. Fig. 3a–d presents the obesity and "overweight + obesity" (BMI $\geqslant$ 25) percentages in adults for each database. These percentages substantially increase from earlier databases to later ones, but the data are comparable between corresponding SSB frequent and infrequent users in each database. Taken together, the data suggest that usual SSB consumption by itself has little contributory effect on obesity occurrence.

3.2. SSB, fat and energy intakes

Tables 2–4 present the intakes of SSB, energy and % fat energy between obese and non-obese populations. The means of SSB intakes were calculated using both of original data and power-transformed data. Generally and in this case, the means calculated from original data can represent actual consumption in the population more accurately without regard to the data distribution, while the means from transformed data can characterize a "typical" consumption distribution more accurately. Whether one uses the original or transformed data mean depends upon your intended application of the data. In the current work, the main focus was not to investigate the SSB consumption distribution, and, the outcomes for the analysis of obesity risk would not be influenced by selecting one method over the other to calculate the SSB intake means. We did find the presence of a small portion of very high consumers skewed the distribution such that the original data means were 13–40% higher than the means of the transformed data. Although this skewing did not alter the conclusions in our analysis for comparisons within a data set, it could have a significant impact if one were to use original data means as characteristic of SSB usual intakes. Both transformed and non-transformed data for SSB consumption means are presented in Tables 2–4.

We found a second anomalous bias when comparing the CSFII databases with the NHANES databases. After calculating the SSB consumption means for the various databases, we noted that the NHANES III data was much higher than the corresponding CSFII data. As we defined

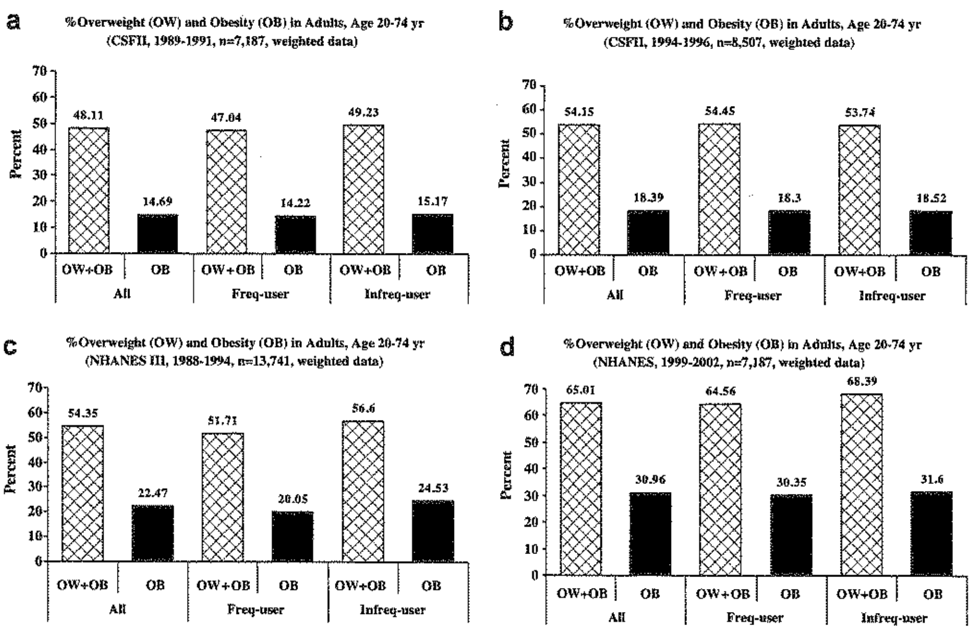

Fig. 3. Obesity and overweight occurrence in adults (weighted data).

Table 2
SSB, energy, and fat intakes and the intake comparison between survey period and SSB consuming-day only data in adults, age 20–74 (mean(SD)), weighted data, CSFII 1989–1991

Variable	Survey period (3 days) data		Only consuming day(s) data		Ratios of consuming-day only to survey period data	
	BMI < 30 ($n = 3897$)	BMI => 30 ($n = 768$)	BMI < 30 ($n = 3897$)	BMI => 30 ($n = 768$)	BMI < 30	BMI => 30
SSB (g)	391.13 (348.72)	376.45 (303.27)	522.85 (338.42)	522.96 (279.9)	1.337	1.389
SS B (g)-2[a]	295.22 (16.67)	288.77 (15.32)	455.81 (35.02)	465.54 (35.59)	1.544	1.612
Sugars from SSB (g)	41.37 (36.67)	39.7 (31.77)	55.38 (35.7)	55.24 (29.41)	1.339	1.391
Energy (kcal)	2017.69 (764.81)	1935.47 (795.33)	2019.3 (764.13)	1936.33 (794.31)	1.001	1.000
% SSB kcal	8.58 (7.89)	8.87 (7.51)	11.77 (8.34)	12.65 (8.27)	1.372	1.426
% Fat kcal	34.59 (6.98)	35.94 (6.76)	34.32 (7.02)	35.53 (6.88)	0.992	0.989
% Satu. fat kcal	12.15 (3.15)	12.27 (2.91)	12.05 (3.16)	12.12 (2.91)	0.992	0.988
BMI	23.91 (3.09)	34.03 (4.58)	23.91 (3.09)	34.03 (4.58)	1	1

[a] Data obtained from power-transformed SSB intake values.

Table 3
SSB, energy, and fat intakes and the intake comparison between survey period and SSB consuming-day only data in adults, age 20–74 (mean(SD)) weighted data CSFII 1994–1998

Variable	Survey period (3 days) data		Only consuming day(s) data		Ratios of consuming-day only to survey period data	
	BMI < 30 ($n = 3705$)	BMI => 30 ($n = 935$)	BMI < 30 ($n = 3705$)	BMI => 30 ($n = 935$)	BMI < 30	BMI => 30
SSB (g)	514.23 (468.78)	498.39 (474.57)	638.05 (488.06)	630.68 (480.21)	1.243	1.267
SS B (g)-2[a]	386.02 (31.09)	389.44 (30.41)	529.36 (33.87)	540.21 (32.88)		
Sugars from SSB (g)	54.66 (49.41)	52.85 (49.9)	67.96 (51.68)	66.94 (50.42)	1.371	1.387
Energy (kcal)	2245.81 (924.84)	2123.8 (889.15)	2303.81 (981.67)	2199.27 (983.55)	1.026	1.036
% SSB kcal	10 (8.03)	10.37 (8.21)	12.82 (8.7)	13.27 (8.6)	1.282	1.280
% Fat kcal	32.9 (7.41)	33.98 (7.18)	32.18 (8.16)	33.19 (8.02)	0.978	0.977
% Satu. fat kcal	11.02 (3.16)	11.51 (3.09)	10.79 (3.4)	11.2 (3.37)	0.979	0.973
BMI	24.32 (3.04)	34.53 (4.74)	24.32 (3.04)	34.53 (4.74)	1	1

[a] Data obtained from power-transformed SSB intake values.

Table 4
SSB, energy, and fat intakes (mean(SD), weighted data, NHANES)

Variable	NHANES III 1988–1994		NHANES 1999–2002		Potentially over-estimated (%)[a]	
	BMI < 30 ($n = 5165$)	BMI => 30 ($n = 1788$)	BMI < 30 ($n = 2542$)	BMI => 30 ($n = 1213$)	BMI < 30	BMI => 30
SSB (g)	653.28 (463.94)	693.97 (494)	798.89 (654.77)	871.01 (631.09)	33.7	38.9
SS B (g)-2[b]	520.94 (35.45)	555.37 (37.93)	606.04 (47.01)	682.56 (50.54)		
Sugars from SSB (g)	70.14 (50.36)	74.29 (52.96)	85.95 (70.91)	93.69 (68.87)	33.9	39.1
Energy (kcal)	2495.42 (1162.64)	2315.88 (1049.56)	2496.39 (1122.63)	2428.63 (1033.45)	–	–
% SSB kcal	11.87 (8.55)	13.43 (9.15)	14.11 (10.26)	16.05 (10.46)	37.2	42.6
% Fat kcal	33.12 (8.98)	33.88 (8.85)	31.43 (8.81)	32.86 (8.72)	–	–
% Satu. fat kcal	11.38 (3.89)	11.57 (3.68)	10.39 (3.65)	10.83 (3.62)	–	–
BMI	24.06 3.14	35.17 5.32	24.68 3.15	35.77 5.49	–	–

[a] Based on the data obtained from CSFII 1989–1991 (Table 2).
[b] Data obtained from power-transformed SSB intake values.

frequent users to be consumers anytime during the survey period, NHANES data would contain only users consuming SSB on the one day surveyed, while users in the CSFII database may be consumers on 1 and/or 2 and/or 3 of the survey days. Since the total consumption for the survey period was averaged over the number of survey days, inconsistent consumers would be included, but their average daily consumption would be less than those identified on a single day only survey. To further test this effect, we analyzed each CSFII dataset by comparing consuming day only values with the averaged consumption values for the entire survey period. The overestimation found from using consuming day(s) only data versus survey period data was between 24% and 39% (Tables 2 and 3), with overestimates being slightly higher for the BMI ⩾ 30 groups.

Both sets of CSFII data show little difference in SSB consumption between obese and non-obese adults (Tables 2 and 3), while NHANES data indicated that obese adults had higher SSB intakes (40.7–72.1 g of SSB, or 4.2–7.7 g of sugars/day, or 16.5–30.8 kcal/day) compared to non-obese adults (Table 4). For daily energy intakes, the means of obese adults were found to be either comparable to or lower than the values of non-obese adults for all data sources. Similarly, as shown in Fig. 4, daily energy intakes were not proportionally related to BMI. However, obese adults consistently had somewhat higher fat intakes relative to total calories. Table 5 shows the daily energy intake means by different levels of physical activity. Clearly, the more active population always had a higher energy intake than that of the less active populations. This data suggests that a higher energy intake in a population does not automatically mean an over energy intake, which is the fundamental cause of obesity occurrence.

3.3. Obesity risk

The potential influence of gender, age, education, multiple lifestyle factors and SSB consumption on obesity risk was evaluated using Logistic regression (Logit) analyses. In total, 10 variables were used for the Logit analyses, which included gender, age group, smoker, education, TV watching hours, physical activity, SSB user, % fat intake levels, % saturated fat intakes, and calorie intake levels. The population consisted of 38,005 adults (age 20–74 years) who had complete data records suitable for the analyses. Odds ratios (OR), 95% confidence intervals of OR, and p-values for association with obesity risk were predicted for each explanatory variable in the model. Together with daily energy intake level and saturated fat intake, none of the analytical outcomes from the four datasets (Table 6) indicated that sugar sweetened beverage consumption was a significant explanatory factor for obesity risk covering the 15 year period of the surveys from 1988 to 2002. Gender, age group, smoker, education, TV watching hours, physical activity, and fat intake levels were significantly associated with obesity risk (Table 6).

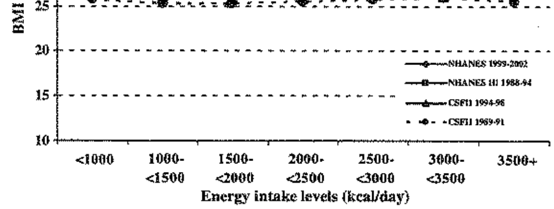

Fig. 4. Daily energy intake levels and BMI in adults (weighted data).

The outcome data in Table 6 provides the odds ratios and statistical p-values for each independent variable, together with more detailed sub-comparisons within a variable that has more than two categories. The outcomes from all four datasets indicate that women appeared to have a higher susceptibility to become obese compared to men (OR from 1.165 to 1.491), especially in recent years. Age group influenced obesity risk with a pattern of upsurge, plateau, then decline. The most obvious obesity risk increase was observed between the age groups 20+ and 30+ years, while the 30+ age groups being 30.9–72.9% more likely to be obese than the 20+ age group. When comparing 50+ to 40+ groups, there was not a significant difference noted. Further, for age groups 60+ or 70+, the obesity odds decreased by 20.1–40.1% in contrast to the younger adjacent age group, except between 60+ and 50+ groups of NHANES 1999–2002 data (the OR was 1.039 and $p = 0.6494$ between them). Smoking habit was found to be a strong factor linked to a lower chance of becoming obese. All data of the four databases showed that adult smokers were 35–40% less likely to become obese compared to non-smokers. The population with a higher education level also had a lower chance of being obese. Compared to lower education levels, more than a high school education population turned out always to be associated with lowered risk by 10.9–45.9%. Sedentary lifestyle had the most apparent influence on obesity risk. For each 2-h additional TV/Screen watching time, the population had a 20.8–54.1% increased chance of being obese. Typically, as shown with NHANES 1999–2002 data, a population with more than 4 h TV/screen time daily doubled their likelihood of being obese compared to a population with 2 h or less the time. The physically active population decreased their odds of being obese by 18–56.7% relative to physically moderate or inactive populations. Dietary fat content was also a meaningful factor linked with increased obesity risk. Each intake level increase of fat calories (<30% to 30–40% to >40%) would lead to 7.9–26.5% higher chance of becoming obese. On the other hand, SSB frequent consumption, dietary saturated fat content, or the level of dietary calorie intake were not factors which had a significant impact on obesity risk in the populations studied. The p-values (from 0.1467 to 0.8212) for Goodness-of-fit tests of the models in Logit analyses indicated that the dependent variable-obesity status was satisfactorily explained by the explanatory variables for all the databases.

Table 5
Mean calorie intakes by physical activity in adults, age 20–74 (kcal/day, mean (SD), weight data)

Physical activity	CSFII 1989–1991, $n = 8974$	CSFII 1994–1996, $n = 8507$	NHANES III 1988–1994, $n = 13741$	NHANES 1999–2002, $n = 7187$
Active	2105.97 (916.58)	2255.9 (1003.23)	2361.2 (1319.06)	2351.11 (1075.06)
Moderate	1811.39 (746.14)	2044.33 (828.31)	2244.64 (1058.05)	2328 (1015.53)
Minimal	1749.98 (686.6)	1885.08 (778.82)	2171.01 (984.36)	2174.24 (1050.06)

Table 6
Logistic regression analysis outcomes for obesity risk in adults (age 20–74 years)[a]

Independent variables	CSFII 1989–1991 ($n = 8860$)		CSFII 1994–1996 ($n = 8364$)		NHANES III 1988–1994 ($n = 13{,}594$)		NHANES 1999–2002 ($n = 7187$)	
	OR (95% CI)	*p*-Values	OR (95% CI)	*p*-Values	OR (95% CI)	*p*-Values	OR (95% CI)	*p*-Values
Gender (F to M)	1.209 (1.063–1.375)	**0.0039**	1.145 (1.01–1.297)	**0.0341**	1.451 (1.328–1.585)	**<0.0001**	1.477 (1.323–1.65)	**<0.0001**
Age groups		**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**
30+ to 20+	1.621 (1.345–1.953)	<0.0001	1.401 (1.14–1.723)	0.0014	1.729 (1.526–1.9588)	<0.0001	1.303 (1.092–1.554)	0.0033
40+ to 30+	1.366 (1.153–1.619)	0.0003	1.416 (1.187–1.689)	0.0001	1.299 (1.153–1.4652)	<0.0001	1.278 (1.086–1.503)	0.0031
50+ to 40+	0.963 (0.798–1.161)	0.693	0.951 (0.806–1.121)	0.5519	1.068 (0.933–1.2215)	0.336	0.932 (0.79–1.1)	0.4081
60+ to 50+	0.799 (0.658–0.971)	0.0241	0.759 (0.64–0.901)	0.0016	0.783 (0.681–0.9011)	0.0006	1.039 (0.879–1.229)	0.6494
70+ to 60+	0.599 (0.455–0.789)	0.0003	0.654 (0.504–0.85)	0.0015	0.74 (0.621–0.8818)	0.0008	0.711 (0.574–0.88)	0.0018
Smoker (Yes to No)	0.612 (0.535–0.699)	**<0.0001**	0.648 (0.568–0.739)	**<0.0001**	0.594 (0.541–0.652)	**<0.0001**	0.632 (0.558–0.715)	**<0.0001**
Education		**<0.0001**		**<0.0001**		**<0.0001**		**0.0433**
High-S to <High-S	0.831 (0.725–0.952)	0.0078	0.764 (0.659–0.886)	0.0004	0.95 (0.864–1.0449)	0.2938	1.025 (0.894–1.176)	0.7184
>High-S to High-S	0.798 (0.691–0.921)	0.0021	0.707 (0.622–0.804)	<0.0001	0.752 (0.678–0.8339)	<0.0001	0.86 (0.753–0.982)	0.026
>High-S to <High-S	0.663 (0.57–0.772)	<0.0001	0.541 (0.463–0.631)	<0.0001	0.714 (0.644–0.7927)	<0.0001	0.882 (0.78–0.998)	0.047
TV/screen hours		**<0.0001**		**<0.0001**		**No data**		**<0.0001**
2–4 to <2	1.298 (1.112–1.513)	0.001	1.33 (1.173–1.508)	<0.0001	–	No data	1.305 (1.153–1.478)	<0.0001
>4 to 2–4	1.308 (1.149–1.489)	<0.0001	1.208 (1.03–1.416)	0.02	–	No data	1.546 (1.367–1.747)	<0.0001
>4 to <2	1.698 (1.446–1.994)	<0.0001	1.607 (1.379–1.873)	<0.0001	–	No data	2.018 (1.756–2.321)	<0.0001
P activity		**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**
Moderate to minimal	0.636 (0.563–0.718)	<0.0001	1.014 (0.868–1.184)	0.8541	0.853 (0.705–1.033)	0.1043	0.799 (0.703–0.909)	0.0006
Active to moderate	0.68 (0.54–0.857)	0.001	0.683 (0.596–0.783)	<0.0001	0.821 (0.718–0.935)	0.0036	0.782 (0.607–1.008)	0.0584
Active to Minimal	0.433 (0.344–0.545)	<0.0001	0.693 (0.603–0.796)	<0.0001	0.599 (0.528–0.68)	<0.0001	0.629 (0.538–0.736)	<0.0001
SSB user (Freq. to Infreq.)	1.003 (0.89–1.131)	**0.955**	1.109 (0.987–1.247)	**0.0831**	1.06 (0.975–1.152)	**0.1742**	1.084 (0.973–1.209)	**0.1448**
Fat intake levels		**0.0019**		**0.0045**		**0.0004**		**<0.0001**
30–40% to <30%	1.257 (1.022–1.546)	0.030	1.079 (0.928–1.255)	0.3196	1.132 (1.019–1.2571)	0.0205	1.191 (1.046–1.356)	0.0081
>40% to 30–40%	1.229 (1.057–1.428)	0.007	1.265 (1.087–1.472)	0.0023	1.159 (1.042–1.2894)	0.0064	1.243 (1.076–1.437)	0.0031
>40% to <30%	1.545 (1.204–1.982)	0.001	1.366 (1.112–1.677)	0.0029	1.312 (1.145–1.5035)	<0.0001	1.481 (1.239–1.771)	<0.0001
Satu. fat intake level	0.973 (0.784–1.206)	**0.8333**	1.087 (0.972–1.215)	**0.1447**	0.995 (0.925–1.07)	**0.8917**	1.015 (0.922–1.116)	**0.7468**
Kcal level	0.985 (0.935–1.036)	**0.5518**	0.999 (0.957–1.043)	**0.9595**	0.977 (0.951–1.004)	**0.0971**	0.979 (0.946–1.013)	**0.2143**
Goodness-of-fit		**0.7154**		**0.8212**		**0.1467**		**0.4932**

[a] OR = odds ratios for obesity; age groups divided by a 10-years interval; Smoker = current smoker or not; Education = less, equal, or more than high school; TV/screen hour =< 2, 2–4, or >4 h/day; P activity = physical activity at active, moderate, or minimal level; Freq. and Infreq. = frequent and infrequent; fat intake level =< 30%, 30–40%, or >40% of daily energy from fat; Satu. fat level =< 10, 10–15, or >15% of daily energy from saturated fat; Kcal level = daily calorie intake at <1000, 1000 ⩽ 1500, 1500 ⩽ 2000, 2000 ⩽ 2500, 2500 ⩽ 3000, 3000 ⩽ 3500 or ⩾3500; and goodness-of-fit = testing a model if it lacks of goodness-of-fit, a non-significant *p*-value indicates model has a good fit for data, that is, dependent variable can be satisfactorily explained by independent variables.

Table 7
Fasting plasma leptin concentration (ng/ml) in adults, from NHANES III

	N	Mean	Weighted mean	SD
SSB user				
Infrequent user	3358	12.66	11.90	11.30
Frequent user	3057	12.47	11.34	12.36
Gender				
Men	2937	6.08	6.01	5.12
Infrequent user	1468	6.41	6.20	5.21
Frequent user	1469	5.76	5.82	5.00
Women	3478	18.05	16.61	13.04
Infrequent user	1890	17.52	16.29	12.33
Frequent user	1588	18.68	17.05	13.82

3.4. Leptin concentrations

Recent studies have suggested leptin concentrations may be modulated by fructose consumption (Teff et al., 2004). The NHANES III database contains fasting serum measurements of some biochemical markers, including the hormone leptin. Leptin concentration means were calculated between adult SSB users (frequent or infrequent) and by gender. The data in Table 7 indicates that the leptin levels are virtually identical between adults with various SSB consumption patterns (means = 12.47 and 12.66, medians = 11.34 and 11.90 ng/ml, for frequent and infrequent users of SSB, respectively). The leptin mean in male frequent users was slightly lower than the value of infrequent users, and this scenario was reversed in women. Moreover, women had almost a three times higher leptin concentration mean than that of men (18.05 and 6.08 ng/ml, respectively). Assuming the users surveyed were chronic users, this data would suggest leptin levels measured in fasting serum were not influenced significantly by SSB consumption. The data do not address acute, high dose administration effects of pure fructose or fructose from SSB, however.

4. Discussion

The recently released NHANES 2003–2004 data indicate that the obesity rate has increased another 1.8% compared to the rate of NHANES 1999–2002 in adults, age 20–74 (from 30.96% to 32.76%, weighted data, analyzed by the authors). The issue of added sugars in the diet and their potential influence on health, in particular obesity, has created a substantial controversy in nutrition, political and policy circles. As a reaction to various reports, recent nutrition guidelines have recommended reducing intakes of added sugars (especially SSB) (USDA), school systems are limiting access to or banning vending machines, and food formulators are being pressured to remove added sugars from formulations. Considerable tax dollars are now being spent on research to determine how various added sugars are being metabolized. As more detailed physiological mechanisms and nutrition theories are elaborated, the ability to assess a meaningful relationship between a single dietary factor and a physical or medical outcome becomes more complex. Understanding the observational significance of an isolated biomarker can be difficult within the context of human homeostatic energy balance, interactive metabolic and neuroendocrine pathways, and net sugar carbon utilization. Along with advances in statistical theory and computing tools for analyzing biological effects of dietary factors, answers to questions about how individual food components affect obesity occurrence are likely to become more assessable.

In this paper, descriptive statistics and logistic regression of population survey databases over a 15-year period were used to phenomenologically examine how multiple lifestyle factors and consumption pattern of sugar-sweetened beverages are related to BMI value and obesity risk. Outcomes of the analysis indicate no substantive differences in BMI and rates of obesity occurrence between frequent users and infrequent users of sugar-sweetened beverages and among energy intake levels (Figs. 1–4). Between obese and non-obese adults, SSB intake amount is essentially identical in all databases except in NHANES 1999–2002 (Tables 2–4). In NHANES 1999–2002, obese adults had a mean sugar sweetened beverage intake of 72 g/day more than the mean intake value of non-obese adults. The difference of SSB intake represents about 9% or 7.7 g sugars (31 kcal). However, in consideration with other factors that potentially influence obesity occurrence as indicated in the risk analysis, the noted frequent SSB intake in obese adults was not sufficient to be a significant factor for elevating obesity risk (Table 6).

The higher energy intakes were not accompanied with higher BMI values or obesity rates (Fig. 4 and Table 1). This would suggest that high energy intake does not necessarily equate to an over-energy intake on a population basis. Populations with higher energy intake without accompanying higher BMI may partially be explained by individuals being engaged in higher energy expenditure (e.g. heavy laborers, athletes, and regular exercisers). The data in Table 5 show that physically active people did indeed have much higher energy intakes. These data simply indicate that the obese population is not required to have a higher energy intake level compared to the non-obese population and that a person who has higher energy intake is not necessarily obliged to have an excess energy intake. An alternative explanation may be that some obese people were on lower calorie diets or stopped consuming SSB, and therefore, would be counted as SSB infrequent users. If this possibility were true, the relevant statistical outcome could be potentially influenced. On another point, we observed that the adults with the lowest calorie intake (<1000 kcal/day) had the highest percentages of obesity, with the exception of CSFII 1989–1991 data (Table 1). The lower energy intake level could also be caused by under reported food intake amounts and this could further cause a bias in the risk analysis. To test this, we further performed risk analysis by excluding individuals in the lowest energy intake group. SSB consumption pattern and energy intake levels were still not significant factors for obesity risk (data not presented). Therefore, energy intake alone can not be a reliable factor for evaluating risk of obesity occurrence without energy expenditure balance data. Factors that do significantly impact obesity rate and risk include gender, age, education, smoking habit, physical activity, TV/screen watching hours, and dietary fat content. Although these factors have somewhat different impacts on obesity risk (odds ratios) within and between databases, their effects are the most obvious. Among the four food intake factors used in risk analysis (SSB, fat, saturated fat, and energy), only higher fat intake level significantly increased the risk of obesity occurrence. In addition to the fact that fat can be more efficiently stored by the body than carbohydrates from over consumed energy (Armellini et al., 1996; Horton et al., 1995), a high fat diet, which usually has higher energy density and superior palatability, can induce a person to over consume energy. Although descriptive statistics indicated a trend between saturated fat intake levels and obesity rates (Table 1), the saturated fat intake was not statistically significantly correlated with obesity risk after adjusting for the other factors.

The occurrence of obesity is linked to multiple factors. Thus, a simple statistical analysis is less meaningful because it may mislead when interpreting its outcomes, especially for retrospective data. For example, the population with higher energy intake level generally had a lower rate of obesity, as shown in Table 1; however, we can not suggest that a population with lower energy intake level is more susceptible for obesity based on a statistical significance, or vice versa. The results from model analysis using multiple factors indicated that energy intake was not a significant factor influencing obesity risk, even if there were clear trends from descriptive statistics. Additionally, the explanation of the differences in obesity rates between databases would require extensive analysis and interpretation. For example, the higher obesity rates found in NHANES 1999–2002 may result from many factors, some of which may not be quantified in all databases. This work of comparing environmental, behavior, diet, and other changes between databases would be best treated as a separate paper.

For the noted inconsistency of plateau age of obesity rates between databases (Fig. 1), it is less likely due to imprecise data management or data processing because obesity classification is clear and its statistical calculation is simple. The observed variation of obesity plateau age among databases could result from sampling error, because sample size significantly decreased after grouping by a 5-year interval. Another possibility could be that obesity rates between age groups truly changed over time. We did not investigate the details for the age shift of the obesity plateau. One unexpected outcome was that NHANES III 1988–1994 data exhibited a higher obesity percentage than the later data of CSFII 1994–1996 (Table 1). An explanation for this inverse trend could be due to study design difference and sampling error. Body weight and height data were collected using questionnaires in CSFII while actual measurements were taken in NHANES. It is also possible that some participants under-reported body weights and/or over reported heights.

Nutrition professionals understand that people usually do not consume a particular food item every day, and thus one-day food intake data can be different from the data collected from multiple days (Carriquiry, 2003; Freedman et al., 2004; Hoffmann et al., 2002; Nusser et al., 1996). Using CSFII databases, we compared the values of SSB intakes between consuming day(s) only data and entire survey period data (3 days for CSFII 1989–1991 and 2 days for CSFII 1994–1996) and found that one-day data can overestimate SSB intake by 24–26% compared to 2-day data (Table 3) and by 34–39% compared to 3-day data (Table 2). This suggests that some SSB frequent "users" do not consume SSB every day and that caution is advised when attributing a truly characteristic consumption amount from one-day survey data. We also compared "day-1 only" data with "only consuming day" data for SSB consumption (data details not shown). The day-1 only data are comparable to "only consuming day" data for CSFII 1994–1996. The sampling design could mostly account for the noted similarity (a participant who had 2nd day data must have the 1st day data). For CSFII 1989–1991, day-1 intakes of SSB, SSB-sugar and energy are somewhat higher than the values of only consuming day data (6.2–11.6% for SSB and 7.2–8.6% for energy). Beyond the difference of sampling design (a participant who had 2nd/3rd day data did not have to have the 1st day data), day-by-day variation could account for the noted slight increase. Thus, if comparing day-1 only data to survey period data, the noted overestimation rate for SSB consumption would be greater. Nevertheless, the day-1 only data showed similar obesity rates between frequent and infrequent SSB users (14.25% and 14.96% for CSFII 1989–1991, and 18.74% and 18.46% for CSFII 1994–1996, respectively, weighted data) as the data in Table 1. Therefore, the results of risk analyses were deemed to not be meaningfully influenced. These results further indicate that a food intake survey with a larger number of data collecting days can provide more reliable data, especially for evaluating intakes of a single food item or category, and that population mean intakes obtained from one-day dietary data as NHANES can be significantly over or under estimated.

Commonly, the distribution of intake data for a food item or categorized food is not normal (most likely right skewed). Under these circumstances, the means or percentiles obtained from original data in users would not be appropriate to describe its "usual intake" in a population. In order to evaluate the population "usual intake" of the food or nutrient intakes from the food, the skewed data should be transformed into normal or approximately normal distribution. Thus, the obtained means can be more accurate to describe the "typical" population intake status, rather than, for example, percentile intakes; and obtained parameters that are variance-related (such as SD or SE) or statistical comparisons that are variance-based (such as t-test or ANOVA) can be valid. The terms of "usual or typical" intake is more often used in nutrition field. On the other hand, the means and percentiles obtained from raw data with skewed distribution are more often used in market volume estimation or food toxicology evaluation. For either situation, the more days data are collected from, the more accurate the means could be. In this study, both of SSB intake means from original data and transformed data are given (Tables 2–4), and its purpose is to better describe SSB intakes. We did not perform any data transformation for the other three dietary variables (% fat energy, % saturated fat energy and total energy) analyzed in this work, because they are nutrient intakes rather than food intakes, data examination showed that they were normally or basically normally distributed, and after categorization, these data would not impact risk analysis.

We noted several reviews related to the issue of SSB consumption and obesity. Two of the three reviews concluded that there is insufficient scientific evidence to support the hypothesis of a SSB-obesity link (Bachman et al., 2006; Pereira, 2006), and one review concluded that SSB is associated with weight gain and obesity (Malik et al., 2006). To compare our data with other prospective, longitudinal, experimental, and/or cross-sectional studies, we reviewed a number of papers which contained sugars consumption data and BMI values. To date, only a few population follow-up studies have been conducted in which one may assess the influence of SSB consumption on obesity risk and BMI changes. Schulze et al. (2004) reported their analysis based on the American Nurses' Health Study II data collected from 1991 to 1999, of 51,603 nurses with initiating age of 24–44 years old. Subgroup analysis provided a continuous SSB user group with high consuming frequency ($\geqslant 1$ SSB drink/day, 2366 nurses), a continuous SSB user group with low consuming frequency ($\leqslant 1$ SSB drink/week, 38,737 nurses), an "other" group (8473 nurses), and two additional groups which switched from low to high consumption as defined above or visa versa. During the more than 8-year follow-up, less than 4% of the nurses changed their SSB consumption patterns from "low to high" (1007 nurses), or "high to low" (1020 nurses). More than 96% of the nurses maintained their SSB consumption patterns either at "low, high, or other". This data suggests that SSB consumption patterns in an adult population are fairly stable, at least in female nurses. Based on this data, the validity of categorizing an individual as SSB frequent user or non-frequent user using 1, 2, or 3-day dietary intake records in our analysis is supported. Secondly, although weight gain across all groups during the 8-year follow-up was observed, no differences in body weight and BMI changes were noted between groups of SSB low consuming, the high consuming, and the other consuming pattern groups which represented more than 96% of the subjects of the study cohort. These observational outcomes support our findings that SSB consumption pattern is not a significant factor on obesity risk and BMI changes.

On the other hand, 1.95% of the cohort (1007 nurses) in Schulze's study, who changed their SSB consumption from low to high, had more weight gain than that of the other groups mentioned above (about 1.5 kg more than the constant consuming group during the first 4 years and 2.0 kg more during the 2nd 4 years). The other 1.98% of the cohort (1020 nurses), who changed their SSB consumption from high to low, had less weight gain (about 2 kg less than the constant consuming groups in each 4-year period). Based on these outcomes from less than 4% of the total study cohort, the authors concluded "Higher consumption of sugar-sweetened beverages is associated with a greater magnitude of weight gain..." However, this conclusion was not reconciled with the data from the 96% of the nurses who did not change their dietary beverage pattern. Also, the baseline BMI means of the nurses who changed their SSB consumption patterns, either from low to high or vice versa, were significantly higher than that of the other nurses. This suggests that the observed moderate difference in weight change in this 4% of nurses could be caused by other factors. Moreover, a 3 kg body weight change is roughly equal to one BMI unit change for a medium-sized adult female. The study did not indicate whether this BMI rise altered the healthy weight status of the individuals. Another cohort follow-up study (Kvaavik et al., 2005) observed no BMI differences among long term, sugar-sweetened carbonated soft drink high consumers, inconsistent consumers, and low consumers after 8 years following-up (1991–1999) in 443 men and women at initial mean age of 25 years old. In this cohort, the mean sugar-sweetened soft drink consumption of high, inconsistent, and low consumers were 965, 257, and 82 g/day in men and 470, 192, and 43 g/day in women, respectively. Mean BMI values of high, inconsistent, and low consumers at end of the follow-up were 25.3, 25.9, and 25.6 in men and 24, 23, and 23.4 in women, respectively. There was no association noted between sugar-sweetened soft drink consumption and BMI changes.

To further support our findings, several additional studies have been published which examine the effect of dietary added sugar consumption on population health endpoints. Although these studies were not conducted to rigorously examine the relationship between SSB/sugar consumption and body weight per se, the reported data can be examined as to its consistency with the findings herein. Janket et al. (2003) examined the influence between the intake levels (quintiles) of sugars and the incidence of type 2 diabetes in 38,480 women from the Women's Health Study. These authors reported that women in the higher baseline intake quintile of sucrose and total carbohydrates had the lower BMI mean. Wu et al. (2004) investigated the influence of dietary carbohydrate load on C-peptide concentrations in women ($n = 1199$). Their data indicated that the percentage energy from sucrose increased from 7.5% to 8.8% to 10.4% across the first, third and fifth quintile respectively. Percentage energy from free fructose increased from 2.7% to 4.9% to 8.5% across the first, third and fifth quintiles, while energy from total fructose increased from 6.4% to 9.3% to 13.7% in these groups. The mean BMI values for each of the respective quintiles were 26.2, 25.2, and 25.4, respectively. Adjustment for energy and glycemic load did not alter these trends substantially, other than BMI values decreased from first to third and/or to fifth quintile. Consequently, intake levels of sucrose, free fructose, and total fructose loads were negatively correlated or not correlated with BMI. Yang et al. (2003) have reported that higher dietary intake quintiles of carbohydrates, total sugars, and added sugars had no effect or a negative effect on mean BMI values in American adult men and women (age 20 year and over, $n = 11,855$, NHANES III data). Taken together, these reports are consistent with our findings on SSB consumption and body weight status.

In the present analysis, the logistic regression excluded youths under age 20. Several published prospective or cross sectional studies in this population may provide insight on the effect of SSB use and obesity occurrence. Rajeshwari et al. (2005) investigated the potential link between SSB consumption and BMI in 10-year old children ($n = 1548$) from 1973 to1994. Over the seven data collection periods during the 20 years, they noted that there were no significant BMI differences among groups who consumed SSB in either the first, the second, or the third tertile of consumers. Berkey et al. (2004) also reported that SSB consumption was not a significant explanatory factor for yearly BMI change in adolescents aged 9–14 years after adjusting for energy intakes. This analysis included 5067 boys and 6688 girls using data collected over a 2-year period (1996–1998). Forshee et al. (2004) evaluated NHANES III data of 1749 adolescents aged 12–16 years. Their analysis showed that consumption of SSB did not associate with BMI in their models. A significantly negative association with BMI was found for participation in team sports and exercise programs. These authors concluded that reducing sugar sweetened beverage consumption had the smallest impact on reducing BMI.

Conversely, several published reports suggest that SSB consumption may be related to BMI or weight gain. A Denmark study conducted by Raben et al. (2002b) compared the effect of sucrose-sweetened soda and diet soda on weight gain in 41 overweight adult subjects. After feeding the subjects experimental diets for 10 weeks, subjects in sucrose-sweetened soda group (the mean intake of sucrose from soda was 152 g/day) gained 1.6 kg weight and the subjects in the diet soda group lost 1 kg weight. However, the daily energy intake of the sucrose-sweetened soda group was 600 kcal more than that of diet soda group. Over the 10-week period, this would amount to an additional 42,000 kcal intake (600 kcal/day for10 weeks), yet only 1.6 kg (3.52 lb) of weight was gained, or an equivalent about 12,320 kcal. This inconsistency was not explained. Ludwig et al. (2001) observed 548 children with a mean age 11.7 years for 19 months to determine if SSB consumption was linked to BMI. It was noted that the mean SSB intake changed from 1.22 to1.44 servings/day after the 19 months and the percentage of obesity changed from 27.4% to 27.7%. There, obesity was defined as $\geqslant 85\%$ of age–gender specified BMI and triceps skinfold thickness. This differs from the obesity definition from the US CDC and American Obesity Association. The risk analysis showed that SSB consumption was not a significant factor for obesity risk from baseline data, but the serving increase of SSB consumption from baseline was a significant one.

Lastly, the leptin data are intriguing from the standpoint that recent publications have hypothesized (Teff et al., 2004) that long-term consumption of fructose leads to attenuated leptin levels. Lowered leptin levels in turn are purported to lead to a reduction in satiety with the physiological consequence of inducing individuals to overeat. The NHANES III data suggests that fasting leptin levels are not related to consumption of dietary fructose contained in SSB (Table 7). If a direct metabolic relationship between SSB intake and fasting leptin concentrations existed, the mean leptin value for the frequent users should be lower than that of infrequent users. The obvious higher leptin concentration in women could be partially due to their higher percent body fat and noted obesity rate. Some dietary studies reported that high carbohydrate (simple or complex) diet either increase or maintain plasma leptin concentrations (Havel et al., 1999; Raben et al., 2003; Raben et al., 2002a; Romon et al., 1999, 2003).

There are several limitations to our work. First, the dietary intake data in the databases were obtained from dietary recall questionnaires. It is possible that the intake amounts were under reported. Secondly, the body weight and height data in CSFII data were also self-reported data. So, the CSFII data may not be as accurate as the data of NHANES, where weight and height were measured. Thirdly, the SSB consumption patterns can not be absolutely categorized as "user" or "non-user", because the portion of adults who consumed SSB either every day or not at all would be very small. And lastly, although SSB represent a significant portion of dietary added sugars, this study does not address the question of whether there is a potential link between added sugar consumption and obesity risk. Added sugars can cover a variety of sweeteners including sucrose, HPCS, syrups, glucose, dextrose, maltose, fructose, and honey. It would be very meaningful to conduct a similar study to examine if there is a link between added sugar intake and obesity prevalence in the future.

In conclusion, statistical analysis and modeling of CSFII and NHANES databases covering survey periods from 1988 to 2002 indicate that the consumption of sugar sweetened beverages, total calorie intake levels and calories from saturated fat were not significant contributors to the obesity occurrence in the adult populations. Gender, age, education level, smoking habit, TV/screen watching hours, physical activity, and dietary calories from total fat were the more meaningful factors associated with obesity risk. This conclusion is additionally supported by data observed in other scientific publications of studies conducted for other purposes. Additionally, the daily intake means obtained from one-day food intake data may significantly overestimate consumption for certain specific food or food categories which are infrequently consumed (such as SSB). The newest population survey data indicate the US obesity prevalence is still under raising. Obesity is a multi-factorial problem which is rooted in a positive balance between energy intake and expenditure. Lifestyle, behavior, and environment appear to have a more dominant role in obesity prevalence than do individual foods.

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Miscellaneous High Fructose Corn Syrup Research

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Comparison of breath testing with fructose and high fructose corn syrups in health and IBS

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Abstract *Although incomplete fructose absorption has been implicated to cause gastrointestinal symptoms, foods containing high fructose corn syrup (HFCS) contain glucose. Glucose increases fructose absorption in healthy subjects. Our hypothesis was that fructose intolerance is less prevalent after HFCS consumption compared to fructose alone in healthy subjects and irritable bowel syndrome (IBS). Breath hydrogen levels and gastrointestinal symptoms were assessed after 40 g of fructose (12% solution) prepared either in water or as HFCS, administered in double-blind randomized order on 2 days in 20 healthy subjects and 30 patients with IBS. Gastrointestinal symptoms were recorded on 100-mm Visual Analogue Scales. Breath hydrogen excretion was more frequently abnormal ($P < 0.01$) after fructose (68%) than HFCS (26%) in controls and patients. Fructose intolerance (i.e. abnormal breath test and symptoms) was more prevalent after fructose than HFCS in healthy subjects (25% vs 0%, $P = 0.002$) and patients (40% vs 7%, $P = 0.062$). Scores for several symptoms (e.g. bloating $r = 0.35$) were correlated ($P \leq 0.01$) to peak breath hydrogen excretion after fructose but not HFCS; in the fructose group, this association did not differ between healthy subjects and patients. Symptoms were not significantly different after fructose compared to HFCS. Fructose intolerance is more prevalent with fructose alone than with HFCS in health and in IBS. The prevalence of fructose intolerance is not significantly different between health and IBS. Current methods for identifying fructose intolerance should be modified to more closely reproduce fructose ingestion in daily life.*

Keywords *bloating, fructose intolerance, functional bowel disorder, high fructose corn syrup, irritable bowel syndrome.*

BACKGROUND

The introduction of high fructose corn syrups (HFCS) as alternative sweeteners to sucrose in the 1960s resulted in a dramatic increase in the monosaccharide form of fructose in the US food supply.[1] HFCS became, and remain, widely used as sweeteners in beverages, dairy products, canned, baked and processed foods worldwide.[2]

Fructose monosaccharide is absorbed by carrier-mediated facilitated diffusion, an energy-independent process. The fructose carrier is a member of the glucose transport (GLUT) family of genes encoding for facilitative sugar transporters and is referred to as GLUT 5[3] and the rate of fructose absorption is between that of mannose and glucose.[4] Sucrose is cleaved to glucose and fructose by sucrase, an enzyme located in the brush border of small intestine enterocytes. For unclear reasons, the absorptive capacity for fructose derived from sucrose exceeds that of fructose monosaccharide. Unabsorbed fructose is fermented by colonic bacteria producing short-chain fatty acids, hydrogen, carbon dioxide and trace gases. Hydrogen must be excreted in breath and flatus and/or consumed by colonic bacteria as it cannot be metabolized by humans. A rise in breath hydrogen (and/or methane) following substrate ingestion is the basis for detecting incomplete fructose absorption and estimating fructose absorptive capacity. The absorptive capacity for fructose in healthy individuals ranged from less than 5 g to greater than 50 g[5] and was both dose and concentration dependent.[5,6]

Fructose intolerance is diagnosed when gastrointestinal symptoms accompany a positive breath test. The

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amount and concentration of fructose used to detect incomplete absorption by breath-testing has varied among studies. The frequency of incomplete fructose absorption increases as the dose and concentration increase. Up to 50% of healthy subjects incompletely absorbed 25 g fructose (10%) and up to 80% incompletely absorbed 50 g.[5–7] Increasing the concentration from 10% to 20% increased the frequency of incomplete absorption from 37.5% to 71.4%.[6] In uncontrolled studies, the prevalence of incomplete fructose absorption (25 g) was higher in patients with functional bowel disorders, i.e. 36–75%[8–11] compared to the prevalence (i.e. 0–50%) reported in healthy subjects.[5–7] Although it has been suggested that fructose intolerance causes gastrointestinal symptoms in some patients,[11] the only controlled study did not demonstrate a higher prevalence of incomplete fructose absorption and gastrointestinal symptoms in irritable bowel syndrome (IBS).[10] Moreover, glucose greatly facilitates fructose absorption in health;[5,7,12,13] and both natural and processed dietary sources of fructose usually contain glucose. FDA Regulation 21, Section 184.1866 requires 'HFCS' to represent the two fractions HFCS-42 and HFCS-55. Although the name suggests otherwise, glucose is the predominant sugar in HFCS-42 (42% fructose, 53% glucose and 5% oligosaccharides).[14] HFCS-55 (42% glucose, 55% fructose and 3% oligosaccharides) contains a small excess of fructose.[14] Thus, breath testing with pure fructose may not reflect fructose ingestion under normal circumstances. Because glucose increases fructose absorption,[5,7,12,13] breath testing with fructose alone may overestimate the true prevalence of incomplete fructose absorption in controls and IBS.

Our hypothesis was that fructose intolerance (i.e. positive hydrogen breath test and gastrointestinal symptoms) would occur more frequently with pure fructose compared to fructose provided as HFCS in healthy subjects and in IBS.

METHODS

This was a double-blind, randomized, crossover study comparing symptoms and fructose absorption after fructose alone to HFCS. The study was approved by and all the procedures followed were in accordance with ethical standards of the Mayo Clinic Institutional Review Board.

Subjects

Twenty healthy subjects were recruited by public advertisement and 30 patients with a functional bowel disorder were recruited from our outpatient practice. All participants had an interview and a physical examination prior to enrolment, and patients underwent appropriate investigations to exclude organic disease.[15] Exclusion criteria for healthy subjects and patients included significant cardiovascular, respiratory, neurological, psychiatric, or endocrine disease; anxiety or depression as assessed by the Hospital Anxiety and Depression Questionnaire;[16] medications likely to affect gastrointestinal motility (e.g. opiates, anticholinergic agents, adrenergic agents and calcium channel blockers); and abdominal surgery (other than appendectomy, cholecystectomy, or hernia repair). In addition, subjects who used antibiotics at any time during a 2-month period before the study were excluded. A validated questionnaire was used to exclude IBS, functional bloating, diarrhoea, or constipation in controls.[17] Subjects were reimbursed for participating in this study.

Breath tests

Subjects were asked to abstain from pastas, legumes, dairy, fruits, fruit juices and products containing HFCS or fructose along with tobacco products and to limit caffeinated beverages (i.e. two per day) for 24 h prior to breath tests. Mints and chewing gum were also not permitted during the 12-h fasting period before the test for both study days. After mouth rinsing with an antibacterial mouthwash, subjects were randomized, in a double-blind fashion, to one of two sugar solutions [i.e. 40 g of fructose in 330 mL of tap water (12%) or 40 g of fructose as 95 g HFCS-55 (77% dry weight) in tap water to total 600 cc (12%)] provided in identical, covered, opaque containers with a straw. The randomization sequence was generated by the study biostatistician (ARZ) and provided to the pharmacy. These fructose concentrations approximate that of cola sweetened with HFCS-55 (some colas are sweetened with sucrose). Subjects were not informed of the volumes of these solutions and neither subjects nor study personnel administering the test were allowed to hold the container. Subjects were asked to consume solutions within 10 min and to remain sedentary during the study.

Breath samples were collected every 30 min after the test meal for 3 h after the sugar solution was given and analysed for hydrogen concentration. End expiratory breath samples were collected in a modified (Haldane-Priestley) bag (Quintron, Milwaukee, WI, USA). A 20 mL sample of air was withdrawn from the bag and injected into a gas chromatography analyser (Quinn Torn Microlyzer Self Correcting Model SC; Quintron) for detecting breath hydrogen levels. Correction factors were used to correct for CO_2 and dead space using industry standards. Incomplete fructose absorption was defined as a rise in breath hydrogen of ≥20 ppm over the baseline value, which is highly specific for identifying carbohydrate malabsorption.[18]

Symptoms

Symptoms were recorded on separate 100-mm Visual Analog Scales (VAS) for each symptom (i.e. abdominal bloating, flatulence, nausea and abdominal pain) at baseline and every 30 min after the test meal for 3 h.[11] These symptom scores were summarized by adding values for each symptom over 3 h. A 10-mm increase in symptom scores for any symptom over baseline was considered abnormal. Because baseline symptom scores averaged <5, the 10-mm absolute increase is greater than the 10% change considered abnormal in previous studies.[19,20] Subjects also recorded the consistency of every bowel movement during the 3-h postmeal period on a Bristol scale.[8] The same procedure was repeated with the other sugar solution 2–7 days later.

Statistical analysis

The prevalence of an abnormal breath hydrogen response after fructose *vs* HFCS were compared separately in controls and in IBS by McNemar's test for paired discrete data. The area under the curve (AUC) for hydrogen breath excretion after fructose and HFCS were compared by paired *t*-tests or signed-rank tests. The relationship between symptoms and the breath hydrogen response was analysed by Spearman's correlation coefficient. The Breslow–Day test was used to compare the association (i.e. between symptoms and a positive breath test) between health and IBS. Statistical analyses were carried out using the SAS software package (SAS Institute, Cary, NC, USA).

The sample size of 20 controls and 30 patients was expected to provide 10 discordant pairs of controls and 16 discordant pairs of patients using conservative estimates based on previous studies. The null hypothesis was that the discordant pairs would be equally split between those intolerant to fructose and not HFCS *vs* the reverse (intolerant to HFCS and not fructose). This hypothesis was tested separately in patients and controls using McNemar's test (applying the exact binomial distribution). Due to the discreteness of the binomial distribution, conservative two-sided α-levels were necessary to select the rejection regions (degree of imbalance) in the anticipated number of discordant pairs for each subject group. For example, there was 81% power to reject the null hypothesis if the true proportion of fructose intolerant but not HFCS intolerant pairs was 0.92 or greater (reject the null at an α-level of 0.021). Similarly, there was 82% power if the true proportion of fructose intolerant but not HFCS intolerant pairs is 0.86 or greater ($\alpha = 0.021$).

RESULTS

Clinical and demographic features

All subjects completed both breath tests. Age, but not gender or BMI, was associated ($P < 0.01$) with subject group (healthy subjects *vs* patients) (Table 1). Patients had symptoms of diarrhoea predominant IBS ($n = 12$), constipation-predominant IBS ($n = 4$), alternating IBS ($n = 10$), or functional diarrhoea ($n = 4$).[21] In addition, 22 patients reported significant abdominal bloating.

Hydrogen breath tests

After fructose, an abnormal breath hydrogen response was observed in 13 of 20 (65%) healthy subjects and in 21 of 30 (70%) patients (Table 1). In contrast to fructose, an abnormal breath hydrogen response was less frequently ($P < 0.01$) observed after HFCS (i.e. in four of 20 (20%) healthy subjects and in nine of 30

Table 1 Demographic characteristics

Variable	Controls ($n = 20$)	Patients ($n = 30$)
Age (years) (mean ± SE)	28 ± 3	41 ± 2
Number of females	14 (60)	21 (60)
BMI (kg m^{-2}) (mean ± SE)	24 ± 1	26 ± 1
Breath hydrogen response		
Abnormal – fructose	13 (65)	21 (70)
Abnormal – HFCS	4 (20)	9 (30)
Abnormal – fructose and HFCS	4 (20)	9 (30)
Normal – fructose and HFCS	7 (35)	9 (30)
Symptoms after fructose		
Flatulence	4 (20)	9 (30)
Bloating	5 (25)	10 (33)
Nausea	2 (10)	8 (27)
Abdominal pain	2 (10)	9 (30)
Symptoms after HFCS		
Flatulence	2 (10)	6 (20)
Bloating	1 (5)	10 (33)
Nausea	0	8 (27)
Abdominal pain	0	9 (30)

All values except age and BMI are *N* (%) of group total. HFCS, high fructose corn syrup; BMI, body mass index.

(30%) IBS patients]. Among subjects who had an abnormal breath test for fructose and HFCS, breath hydrogen peaks were observed 125 ± 12 min (mean ± SEM) after HFCS and 102 ± 9 min after fructose ($P = 0.125$ by sign test).

Four of 13 healthy subjects and nine of 21 patients who had incomplete fructose absorption after fructose alone also had abnormal breath hydrogen responses after HFCS. No subjects had the combination of an abnormal breath hydrogen response after HFCS and a normal breath hydrogen response after fructose alone. Breath hydrogen responses (i.e. peak and AUC) after fructose and HFCS were not different between health and IBS (Fig. 1). The order of testing (i.e. fructose first *vs* HFCS first) did not affect the results of breath hydrogen tests.

Symptoms

Baseline symptom scores (i.e. prior to sugars) averaged <5 for each symptom and were not significantly different between study days (data not shown). After sugar ingestion, overall symptom scores were not significantly different between fructose and HFCS or between healthy subjects and patients (Table 2). Seven of 20 healthy subjects (35%) and 15 of 30 patients (50%) had one or more symptoms (i.e. a ≥10-mm increase in symptom scores over baseline) during a fructose hydrogen breath test, but only two healthy subjects (10%) and only 14 of 30 patients (47%) had one or more symptoms during a HFCS breath test (Table 3). Bloating was the most common symptom after fructose alone.

Taken together, five healthy subjects (25%) and 12 patients (40%) had fructose intolerance as defined by symptoms and an abnormal breath hydrogen response (Table 3). Thus, the odds ratio for an abnormal symptom response to fructose in those with an abnormal breath hydrogen response relative to those with a normal breath hydrogen response was somewhat higher in patients (OR, 2.67; 95% CI, 0.52–13.66) than in controls (OR, 1.56; 95% CI, 0.21–11.37), but this was not statistically significant ($P = 0.68$). No healthy subjects and only two patients (7%) were intolerant to HFCS ($P = 0.72$). However, intolerance was more prevalent after fructose than after HFCS in patients ($P = 0.002$) and to a lesser extent in controls ($P = 0.062$). As there were no controls and only two patients intolerant to HFCS, a comparison of the homogeneity of the intolerance response between controls and patients could not be tested.

Symptom scores for bloating ($r = 0.36$, $P = 0.01$), flatulence ($r = 0.43$, $P = 0.002$), and pain ($r = 0.36$, $P = 0.01$) but not nausea were related to peak breath hydrogen excretion after fructose; this association was not different between health and IBS. In contrast, symptom scores were not correlated with peak breath hydrogen excretion after HFCS.

Four subjects had bowel movements during the 3-h study. Of these four subjects, two had bowel movements on both study days. The two other subjects had bowel movements after fructose or HFCS on one study day only.

DISCUSSION

Previous studies observed incomplete absorption after 50 g of fructose in 37.5%, 58% and 80% of healthy subjects and after a lower threshold (i.e. 25 g) in 36–75% of patients with IBS.[5,6,8,9,11] Confirming these studies, our data demonstrate that a majority of healthy subjects (i.e. 65%) and patients with functional bowel symptoms (i.e. 70%) incompletely absorbed (40 g) fructose when ingested alone.[5–7] In contrast, a lower proportion of healthy subjects (i.e. 20%) and patients (i.e. 30%) incompletely absorbed (40 g) fructose provided as HFCS, which is generally used to sweeten processed foods rather than fructose alone. Moreover, the prevalence of incomplete fructose absorption after fructose alone or after HFCS was not

Table 2 Comparison of symptoms after fructose and HFCS in controls and IBS

Median (IQR) Visual Analog Scales scores (mm)	Bloating		Nausea		Flatulence		Pain	
	F	HFCS	F	HFCS	F	HFCS	F	HFCS
Healthy subjects	3.5 (0, 30.5)	0 (0, 14.0)	0 (0, 13.0)	0 (0, 9.0)	9.5 (0, 31.0)	0 (0, 19.0)	0 (0, 18.0)	0 (0, 13.0)
Patients	18.0 (1, 87)	15.0 (0, 98)	13.0 (0, 29)	7.5 (0, 40)	13.0 (1, 74)	6.0 (0, 38)	14.5 (0, 55)	10.0 (0, 56)

Values represent the cumulative symptom score recorded at six time points over 3 h (i.e. maximum = 400). F, fructose; HFCS, high fructose corn syrup; IBS, irritable bowel syndrome.

Table 3 Comparison of symptoms and breath hydrogen responses in controls and IBS

Variable	Controls (n = 20)	Patients (n = 30)
Normal fructose breath test	7 (35)	9 (30)
Number with symptoms	2/7 (28)	3/9 (33)
Abnormal fructose breath test	13 (65)	21 (70)
Number with symptoms	5/13 (38)	12/21 (57)
Normal HFCS breath test	16 (80)	21 (70)
Number with symptoms	2/16 (12)	12/21 (57)
Abnormal HFCS breath test	4 (20)	9 (30)
Number with symptoms	0/4 (0)	2/9 (22)

Values in parenthesis are in percentage. IBS, irritable bowel syndrome; HFCS, high fructose corn syrup.

significantly different between healthy subjects and IBS. Taken together, these findings suggest that breath testing as commonly practiced (i.e. 25 g or more of pure fructose) may overestimate the prevalence of incomplete fructose absorption in daily life. Perhaps, a smaller test dose (e.g. 10 g) of fructose or HFCS-55 instead of fructose will provide a more specific measure of incomplete fructose absorption, but even HFCS may overestimate the prevalence of incomplete fructose absorption intolerance because HFCS are usually ingested with other foods that contain glucose and may also enhance fructose absorption. Both sugar solutions contained 40 g of fructose, approximating the fructose content of two cans of cola (closer to 44 g). The HFCS-55 study solution used in this study provided an excess (as compared to glucose) of 9.5 g fructose as a 12% solution, mimicking the ingestion of two cans of cola sweetened with HFCS-55 consumed in isolation. While ingestion of 40 g of fructose provided as HFCS may be commonplace in the diet of some individuals, it is extremely unlikely that 40 g of fructose in isolation would be consumed unintentionally. We speculate that the prevalence of incomplete fructose absorption with the other commonly used fraction of HFCS (i.e. HFCS-42) is even lower because it contains an excess of glucose and should be completely absorbed.

Among subjects with an abnormal breath hydrogen test, breath hydrogen excretion peaked at approximately 2 h after the substrate was administered. Indeed, only four of 47 abnormal breath tests were characterized by peak breath hydrogen excretion at 60 min and in only one subject, a control, was peak breath hydrogen excretion observed at 30 min. Although peak breath hydrogen excretion earlier than 60 min after substrate ingestion may be due to small intestinal bacterial overgrowth,[22] this healthy subject also had normal fasting breath hydrogen excretion, arguing against bacterial overgrowth. It is less widely recognized that early breath hydrogen peak excretion may reflect rapid orocecal transit.[23] We did not measure breath methane excretion as only a small proportion of subjects (i.e. 4% in a recent study) exclusively produce methane.[11]

On the basis of uncontrolled studies, it has been suggested that incomplete fructose absorption is more common (i.e. 36–75%) in patients with functional bowel disorders,[8–11] than in healthy subjects (i.e. 0–50%).[5–7] However, our data confirm the findings of the only previous controlled study,[10] which demonstrated that intolerance for a variety of sugars [i.e. lactose (50 g), fructose (25 g), sorbitol (5 g), fructose plus sorbitol (25 + 5 g) and sucrose (50 g)] is not more prevalent in IBS than in health. Despite these findings, it is conceivable that fructose intolerance may contribute to gastrointestinal symptoms in a minority of patients with IBS.

After ingestion of fructose alone, symptoms were correlated to peak breath hydrogen excretion as suggested previously.[8] Symptoms may be caused by intestinal distention due to osmotic effects of fructose and/or by colonic distention, secondary to colonic bacterial fermentation of incompletely absorbed sugars. Visceral hypersensitivity may also explain symptoms after ingestion of fructose in IBS. However, in a previous study, symptoms after ingestion of fructose–sorbitol were not associated with increased perception of jejunal balloon distention.[24] Symptoms were not correlated to breath hydrogen excretion after HFCS, suggesting they are not attributable to colonic

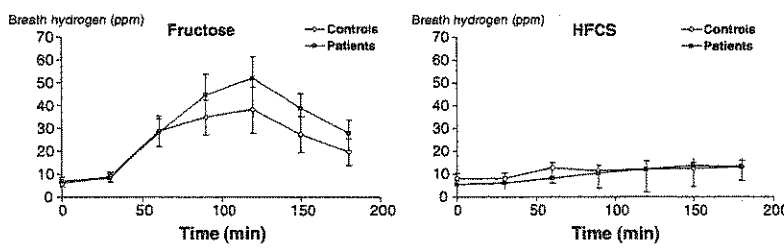

Figure 1 Comparison of breath hydrogen excretion after fructose (left panel) and high fructose corn syrup (HFCS; right panel) in healthy volunteers and patients. Breath hydrogen excretion was not significantly different between healthy volunteers and patients.

fermentation, but may have been due to other factors such as volume.

Glucose increases fructose absorption[5,7,12,13] presumably by solvent drag and passive diffusion.[12,25–27] The extent to which glucose increases fructose absorption depends on the proportion of glucose relative to fructose.[5] An equimolar dose of glucose normalized fructose absorption in healthy subjects[5,13] and glucose at one-half the fructose dose decreased the prevalence of incomplete absorption by over 50%.[5] In addition, it is conceivable that glucose delays gastric emptying, thereby facilitating fructose absorption.[28]

In summary, our data demonstrate that fructose intolerance is more prevalent after fructose alone than after HFCS in health and IBS. The prevalence of fructose intolerance is not significantly different between health and IBS.

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Review

Carbohydrate Issues: Type and Amount

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ABSTRACT

Both the type and amount of carbohydrate found in foods influence postprandial glucose levels and can also affect overall glycemic control in individuals with diabetes. This review, based on the American Diabetes Association's Nutrition Recommendations and Interventions for Diabetes, and the American Dietetic Association's Evidence Analysis Library (Diabetes 1 and 2), provides a description and interpretation of the clinical studies involving diabetes and type and amount of carbohydrate. Although the relationship between blood glucose and insulin is linear, not all types of carbohydrate are fully metabolized to blood glucose. Added sugars such as sucrose and high fructose corn syrup are digested, absorbed, and fully metabolized in a similar fashion to naturally occurring mono- and disaccharides. Only about half of the carbohydrate grams from sugar alcohols and half or less from dietary fiber are metabolized to glucose whereas almost all "other carbohydrate" (mainly starch such as amylose and amylopectin) becomes blood glucose. The percent of energy as carbohydrate indicated for people with diabetes depends on individual preference, diabetes medication, and weight management goals. Glycemic index/glycemic load concepts are attempts to use these carbohydrate availability and amount issues for controlling postprandial glycemia.

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Nutrition (or diet) for individuals with diabetes has always centered around carbohydrates. Before exogenous insulin became widely available, so-called diabetic diets mainly consisted of protein and fats (1). In 1927, Elliott P. Joslin described the optimal diet for a typical patient with diabetes (with or without the help of insulin) as containing 100 g carbohydrate/day (2). Many physicians in the 1920s and early 1930s reported using normal or even high carbohydrate diets. From 1940 to the present, the pendulum has been swinging back and forth concerning the amount of carbohydrate intake that is optimal for people with diabetes. The type of carbohydrate has also been of great interest, with the most extreme being the Kempner rice diet (3). Amounts as well as types of carbohydrate continue to be areas of study.

In the overall schema of the macronutrients, carbohydrates provide the vast majority of glucose for metabolism. The main food carbohydrates can be divided into four general types (see the Figure) (4,5): The monosaccharides and disaccharides (sugars), the oligosaccharides (chains of three to 10 glucose or fructose polymers), and the polysaccharides (with starch and dietary fiber being the main components). There is no question that sugars (ie, glucose, fructose, galactose, sucrose, and maltose) will be digested, absorbed, and influence blood glucose levels postprandially. The picture is less clear for oligo- and polysaccharides because of their complex nature.

Our knowledge of the content (ie, type and amount) of carbohydrates in specific foods comes from two sources: nutritional databases such as the US Department of Agriculture National Nutrient Database for Standard Reference (6), and the Nutrition Facts panel on food labels. The grams of total carbohydrate in foods listed in either of these sources is calculated by "subtraction of the sum of crude protein, total fat, moisture, and ash from the total weight of the food" (7). Other carbohydrate components are obtained by direct chemical analysis.

How foods that contain carbohydrate may differ in terms of absorption, digestion, and metabolism, and how this difference may effect glycemic control, is the topic of this review.

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STATEMENT OF CONFLICT OF INTEREST: See page S38.

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TYPE OF CARBOHYDRATE

Sugars

The term *sugars* is conventionally used to describe the monosaccharides (ie, glucose, fructose, and galactose) and the disaccharides (ie, sucrose, maltose, and lactose) that are absorbed, digested, and fully metabolized (8,9).

The role of added sugars in the diets of people with diabetes continues to be an issue. Added sugars as defined by the Dietary Guidelines for Americans (10) are sugars or syrups added to foods during processing or preparation, and includes common table sugar or sucrose (a mixture of glucose and fructose) as well as other sweeteners like high fructose corn syrups (9). The question for people with diabetes is: Is consuming foods with added sugars (or substituting added sugars for other carbohydrate) detrimental to glycemic control? The American Dietetic Association's Evidence Analysis Library (Diabe-

Type of carbohydrate	Digestion and absorption in small intestine[a]	US food labeling designation
Monosaccharides		
Glucose, fructose, galactose	+	Sugars
Sorbitol, mannitol, etc	+/−	Sugar alcohol
Disaccharides		
Sucrose, maltose, lactose	+	Sugars
Lactitol, maltitol, etc	+/−	Sugar alcohol
Oligosaccharides		
α-Galactosides (eg, raffinose, stachyose)	−	Other carbohydrate
Fructooligosaccharides	−	Other carbohydrate
Maltodextrins	+	Other carbohydrate
Polydextrose	−	Other carbohydrate
Polysaccharides		
Starch (α-glucans)		
Amylose	+/−	Other carbohydrate
Amylopectin	+/−	Other carbohydrate
Modified food starches	+/−	Other carbohydrate
Nonstarch (non-α-glucans) polysaccharides		
Cell wall and chemically related polymers (eg, cellulose, hemicelluloses, pectins, β-glucans)	−	Dietary fiber
Storage (eg, inulins or fructans, guar)	−	Dietary fiber
Plant gums, exudates, and seed mucilages (eg, ispaghula or psyllium)	−	Dietary fiber
Algal polysaccharides	−	Dietary fiber

Figure. Main types of food carbohydrates. [a]Plus sign (+) represents complete/nearly 100% digestion and absorption in the small intestine, whereas plus-or-minus sign (+/−) represents partly digested and absorbed, with the range being very large (2% to 90%), and minus sign (−) represents no digestion and absorption in the small intestine. Adapted with permission from reference 4: *Am J Clin Nutr.* 1995;61(suppl):930S-937S, American Society for Nutrition, and from reference 5: *Am J Clin Nutr.* 1995;61(suppl):938S-945S, American Society for Nutrition.

tes 1 and 2 section) (11) describes two recent studies that provide guidance. A randomized controlled trial (12) lasting 4 months and including 48 adults with type 2 diabetes who were given freedom to add sucrose to their diets at a level of up to 10% of total energy vs a conventional group taught to avoid concentrated sweets found no significant difference in glycosylated hemoglobin (HbA1c) concentrations at the end of the study. A meal-type randomized controlled crossover trial (13), including 10 euglycemic adolescents with type 1 diabetes who were given equivalent carbohydrate meals (one high in sucrose, 35% of energy, and one moderate in sucrose, 17% of energy) and followed for 4 hours postprandially found no significant difference in glycemic responses between the meals.

Based on these and other studies (14-17), the American Diabetes Association recommends that "sucrose-containing foods can be substituted for other carbohydrates in the meal plan or, if added to the meal plan, covered with insulin or other glucose-lowering medications. Care should be taken to avoid excess energy intake" (18).

High fructose corn syrup is widely used as an added sugar in the United States. Two main types of high fructose corn syrup are produced from corn (10): the 42% fructose variety (that also contains 52% glucose) is used mainly in canned fruits, and the 55% fructose variety (40% glucose) is used mainly in soft drinks and desserts. Although an ecologic assessment has suggested that the increased intake of refined carbohydrate (corn syrup), concomitant with decreasing intakes of fiber, paralleled the upward trend in the prevalence of type 2 diabetes (19), no direct link has been found. Two meal-type studies specifically addressed the issue of high fructose corn syrup and type 2 diabetes with differing amounts of fructose and differing results. One study (17 subjects), using 35 g carbohydrate as sucrose, fructose, or high fructose corn syrup (ie, 76% fructose and 21% glucose) found no significant difference between sucrose and high fructose corn syrup meals in either postprandial glucose or insulin responses (20). In the other study, 12 subjects ate 50 g carbohydrate equivalents of glucose, a tofu-based frozen dessert containing high fructose corn syrup (ie, 24% fructose, 29% glucose, and 46% maltodextrin), and a dairy-based ice cream containing sucrose (ie, 67% sucrose, 23% lactose, 6% maltodextrin, and 3% glucose). Peak glucose response and mean glucose area were significantly higher for the high fructose corn syrup-containing dessert than for the sucrose ice cream (21).

The high fructose corn syrup used in most food formulations is roughly half glucose and half fructose, as is sucrose (table sugar) and the same recommendations and cautions that apply to sucrose (above) should be applied to high fructose corn syrup.

Sugars (both naturally occurring and added) are required to be included on the Nutrition Facts panel of food labels as a subcomponent of total carbohydrate (22). Added sugars are not included as a separate line in the Nutrition Facts panel because chemical analyses cannot distinguish between sugars that are naturally occurring

Table 1. Net energy per gram for various sugar alcohols[a]

Sugar alcohol	kcal/g
Erythritol	0.2
Hydrogenated Starch Hydrolysate (HSH)	3.0
Isomalt	2.0
Lactitol	2.0
Maltitol	2.1
Mannitol	1.6
Sorbitol	2.6
Xylitol	2.4
Average sugar alcohol	2

[a]Based on: 1. Federation of American Societies for Experimental Biology. The evaluation of the energy of certain polyols used as food ingredients. June 1994 (unpublished); and 2. Life Sciences Research Office. Evaluation of the net energy value of maltitol. April 1999 (unpublished).

and those that are added to a food. The amount of added sugars in a food can be inferred by the nature of the food itself, its total sugar content, and the prominence of added sugars in the ingredient statement.

Sugar Alcohols (Polyols)

Sugar alcohols (the alcohol forms of mono- and disaccharides, also known as polyols) are also considered sugars (mono- and disaccharides). They have been approved by the Food and Drug Administration as generally recognized as safe or as food additives and are used by food manufacturers to fully or partially replace added sugars in foods, as well as to serve as bulking agents. In studies (generally one meal type) comparing sugar alcohols to similar amounts of fructose, sucrose, or glucose in individuals with diabetes, the sugar alcohols produce significantly lower postprandial glucose responses. For a summary of these studies, visit www.dce.org/links/jada/00346.htm. For example, when 50 g/m^2 body surface area of a hydrolysated starch hydrosylate (ie, 7% sorbitol, 60% maltitol, and 33% oligosaccharides) was compared with the same amount of glucose during a 5-hour period, glycemic response was significantly less for the hydrolysated starch hydrosylate for people with both type 1 and type 2 diabetes (23). Similar results are found for other hydrolysated starch hydrosylates (24), isomalt (25,26), and sorbitol (27,28). One study indicated that erythritol does not produce a glycemic response (29). Although lactitol, mannitol, and xylitol have not been tested in individuals with diabetes, challenge studies with individuals without diabetes indicate a similar lowered glycemic response for lactitol (30), xylitol (30), and mannitol (31).

Based on these and other studies indicating only partial absorption from the small intestine, the US Food and Drug Administration has allowed specific sugar alcohol energy values (Table 1). Sugar alcohols may be voluntarily declared on the Nutrition Facts panel of a food label, but if a claim is made they must be declared. If they are declared, the full amount (grams) of sugar alcohols per serving must be included as a subcomponent of the total grams of carbohydrate on the Nutrition Facts panel of a food label (32); however, in deriving energy value for food labeling purposes, they may be calculated as having half the energy (2 kcal/g) (Table 1) of most other carbohydrates (4 kcal/g).

Other Carbohydrates (Oligosaccharides and Starches)

Other carbohydrates are defined for food labeling purposes as the part of carbohydrate that is not sugars, sugar alcohols, or dietary fiber: oligosaccharides (a very small amount of the food supply) and the starches amylopectin and amylose. They are voluntarily included in the other carbohydrates subcomponent of the total carbohydrate section of Nutrition Facts panels (33).

Amylopectin, containing both linear and branched glucose polymers, makes up about 70% to 80% of starches, and is quite rapidly digested. Amylose, a linear set of glucose polymers, makes up about 20% to 30% of starches, is less rapidly digested than amylopectin, and is prone to form resistant starch. Resistant starch is naturally occurring (nondigestible oligosaccharides), or can be produced by the modification of starch during the processing of foods (9). Legumes are the major food source of resistant starch in the diet (2 to 3 g/100 g cooked weight) (34). Uncooked cornstarch (6 g/100 g dry weight) is another source, with short-term studies focusing on its potential to prevent nighttime hypoglycemia (35). It has not been established that bedtime cornstarch snacks are more effective in preventing nocturnal hypoglycemia than other types of carbohydrates (35), and there have been no published long-term studies in subjects with diabetes to prove benefit from the use of resistant starch (18).

Dietary Fiber

Dietary fiber is nonstarchy polysaccharides and lignin that are not digested by enzymes in the small intestine and typically refers to nondigestible carbohydrates from plant foods (10). Because dietary fiber is not digested in the human small intestine it is not considered a part of the immediate glucose supply. However, colonic bacteria ferment much of the viscous-type fiber to short-chain fatty acids. Acetate and butyrate have no effect on glucose turnover rate but propionate is gluconeogenic in human beings. Current data indicate that the yield is in the range of 1.5 to 2.5 kcal/g (9).

An adequate intake for dietary fiber is 14 g/1,000 kcal/day for adults (9). Table 2 indicates that the median intake in the United States is substantially less then recommended. There does not appear to be a different requirement for people with diabetes compared to those without diabetes.

The American Dietetic Association's Evidence Analysis Library (Diabetes 1 and 2 section) indicates there is inconclusive evidence that increasing dietary fiber above recommended levels will influence glycemic outcome in people with diabetes. For a list of randomized controlled trials that examined this relationship, visit www.dce.org/links/jada/00346.htm. Three randomized controlled trials lasting 6 to 24 weeks and having the same percentages of energy from carbohydrate, fat, and protein for both high fiber (44 to 50 g/day) and low fiber (15 to 24 g/day) diets found no significant difference in HbA1c concentration between diets in well-controlled subjects with type 1 and

Table 2. Recommendations and intakes for dietary fiber by US adults aged ≥19 y

Dietary fiber	Recommendation/ intake
Adequate Intake[a] (g/kcal)	14/1,000
Adequate Intake based on median energy intake[ab] (g/d)	
Men: 19-50 y	38
≥51 y	30
Women: 19-50 y	25
≥51 y	21
Median intake[c] (g/kcal)	6.4/1,000
Median intake for people with diabetes[d] (g/kcal)	7.6/1,000

[a]Adapted from reference 9.
[b]Adequate Intake for total fiber was set for each age and sex group by multiplying 14 g/1,000 kcal/d times median energy intake (kcal/1,000kcal/d). The highest median energy intake level for each group (from the Continuing Survey of Food Intakes by Individuals (1994-1996, 1998) was used in the equation (9).
[c]National Health and Nutrition Examination Survey 2003-2004 data (unpublished): All subjects (n=4,923) aged 18 years or older with reliable dietary recall; adjusted with SUDAAN (version 9.0, 2004, Research Triangle Institute, Research Triangle Park, NC).
[d]National Health and Nutrition Examination Survey 2003-2004 data (unpublished): Subjects with self-reported diabetes (n=479) aged 18 years or older with reliable dietary recall; adjusted with SUDAAN (version 9.0, 2004, Research Triangle Institute, Research Triangle Park, NC).

type 2 diabetes (36-38). When the Giacco and colleagues study (38) excluded noncompliant individuals, compliant subjects reduced their HbA1c concentrations by a small but significant amount (8.6 % vs 9.1%). In one study of children with poorly controlled type 1 diabetes, Kinmouth and colleagues (39) found no significant difference in glycosylated hemoglobin concentration between the high fiber group (60 g/day) and the lower fiber group (20 g/day) at 6 weeks. In terms of daily blood glucose benefits, three studies (36,38,39) found 24-hour glycemic profiles significantly lower on the higher fiber diet vs the lower fiber diet and one study (40) showed significantly lower postprandial glucose levels on the higher fiber vs the lower fiber diet during one meal.

Higher fiber diets are associated with significantly lower total cholesterol vs lower fiber diets, with seven studies (36,37,41-45) showing a significant decrease in total cholesterol in the higher fiber group (average of studies, 50 g fiber per day) compared to the lower fiber group (average of studies, 17 g fiber per day).

Based on studies such as the above, the American Diabetes Association recommends that, although evidence is lacking to recommend a higher fiber intake for people with diabetes than for the population as a whole, people with diabetes should be encouraged to consume a variety of fiber-containing foods to meet the Dietary Reference Intake's adequate intake level per day (18). Following this recommendation may provide benefit in terms of lipid levels and postprandial glycemia.

Dietary fiber is listed on the Nutrition Facts panel of food labels as a subcomponent of total carbohydrate. In the current food labeling regulations, the grams of dietary fiber are counted as part of the total carbohydrate (46); however, in calculating energy, manufacturers may subtract insoluble fiber grams from the carbohydrate grams, but not soluble fiber grams (47).

AMOUNT OF CARBOHYDRATE

The Recommended Dietary Allowance for carbohydrate is set at 130 g/day for adults and children, based on the average minimum amount of glucose used by the brain (9). This is a minimum recommendation, and usually is exceeded to meet energy needs. The median intake of carbohydrates is approximately 220 to 330 g/day for men and 180 to 230 g/day for women, averaging about 49% to 50% of energy, with a recommended acceptable range of 45% to 65% of energy (9). Because carbohydrate intakes outside this range may increase the risk for coronary heart disease and obesity, carbohydrate intakes <45% of energy may not be consistent with adequate intakes of dietary fiber and may be too high in fat, and because carbohydrate intakes >65% of energy may be too low in fat/protein (9) it is reasonable that people with diabetes follow these recommendations. No upper limit of carbohydrate per day is specified by the Dietary Reference Intakes.

Two methods of managing dietary carbohydrate can result in improved glycemic control for people with diabetes: adjusting bolus insulin to match the dietary carbohydrate at each meal; and day-to-day consistency in carbohydrate intake if not taking insulin, or if not adjusting insulin on a meal-to-meal basis (11). Research pertaining to the first method has indicated that people with diabetes can maintain or improve glycemic control without being constrained to eat a specific amount of carbohydrate at each meal (48,49); however, the caveat is that the carbohydrate should cover energy needs without being excessive (eg, producing undesired weight gain). This method is usually based on estimating the grams of carbohydrate in the foods being eaten, and relating that to the insulin bolus dose. Research concerning the second method has also indicated improved glycemic control (50).

Neither of the above methods designates a specific percent of energy as carbohydrate; they are both based on individual preferences, diabetes medication, and maintenance of energy balance.

An attempt has been made to classify individual carbohydrate foods based on the postprandial incremental glucose response and insulin demand they produce for a given amount of carbohydrate (glycemic index) (51-53). A high glycemic index value indicates short full digestion (most/all carbohydrate shows up as glucose in the blood stream within 2 hours), and a lower glycemic index value indicates longer, partial digestion. To indicate the glycemic response to a food, the glycemic index for the specific food (a constant number) and the amount of the carbohydrate in the food both need to be considered (glycemic load). This concept has also been applied to meals, days, and food recall information (54,55). Because the glycemic index, by definition, represents a single identified food it does not reflect, for example, other varieties of the same food (high vs low amylose rice). In addition, fiber, fructose, lactose, and fat in a food or meal have a tendency to lower glycemic response but are not generally considered in the glycemic index or glycemic load formulas. Other potential methodologic problems with the glycemic index have also been noted (56). Although the relationship between glycemic index and metabolic outcomes in persons with diabetes is inconclusive (11), individuals eating high glycemic index diets may find some benefit in controlling postprandial glycemia by switching to a lower glycemic index diet (18).

CONCLUSIONS

Information about both amount and type of carbohydrate is needed for the management of diabetes mellitus. In addition, the percent of energy as carbohydrate for people with diabetes depends on individual preference, diabetes medication, and weight management goals.

Whereas metabolism of glucose is dependent upon insulin (endogenous/exogenous) in a linear relationship, not all dietary carbohydrates are fully metabolized to glucose. The Nutrition Facts panel of a food label provides the total carbohydrate grams contained in a serving of food. The dietary fiber and sugars subcomponents of the total carbohydrate are also included. The sugar alcohols and other carbohydrates (mainly the starches amylose and amylopectin) subcomponents are voluntary; however, if a claim is made for sugar alcohols, it must be included in the Nutrition Facts panel. With this information individuals with diabetes who manage their diabetes by counting carbohydrate grams and adjusting meal insulin boluses can calculate somewhat better estimates of metabolizable carbohydrate.

Sucrose and other added sugars such as high fructose corn syrup, as well sugars naturally occurring in foods, are quickly digested and provide glucose, with the grams being fully counted for carbohydrate gram counting purposes.

Subtracting half or less of the grams of dietary fiber and half of the grams of sugar alcohols (if declared) from the total carbohydrate grams should provide a better estimate of the amount of carbohydrate to be counted toward total carbohydrate for calculating insulin boluses. Practically, only foods containing >5 g dietary fiber or sugar alcohols per serving will make a difference in estimating carbohydrate grams. The other carbohydrates (mainly amylase and amylopectin) should be assumed to be fully metabolized for carbohydrate gram counting purposes.

STATEMENT OF CONFLICT OF INTEREST: The authors have no conflict of interest to report with the sponsor of this supplement article or products discussed in this article.

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AMERICAN MEDICAL ASSOCIATION

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AMA finds high fructose syrup unlikely to be more harmful to health than other caloric sweetners

For immediate release
June 17, 2008

CHICAGO — After studying current research, the American Medical Association (AMA) today concluded that high fructose syrup does not appear to contribute more to obesity than other caloric sweeteners, but called for further independent research to be done on the health effects of high fructose syrup and other sweeteners.

"At this time there is insufficient evidence to restrict the use of high fructose syrup or label products that contain it with a warning," said AMA Board Member William Dolan, MD. "We do recommend consumers limit the amount of all added caloric sweeteners to no more than 32 grams of sugar daily based on a 2,000 calorie diet in accordance with the Dietary Guidelines for Americans."

High fructose syrups are sweeteners produced from starches such as corn, rice and wheat. They can be found in a variety of food products, including breakfast cereals, soft drinks and breads. Currently, there are few available studies on the health effects of high fructose syrup and most are focused on the short-term effects.

"Obesity continues to be a major public health problem in this country. Overweight and obese adults and children are at an increased risk for chronic health conditions like heart disease and diabetes" said Dr. Dolan. "Eating a healthier diet can help maintain a healthy weight and drastically reduce your chances of developing weight-related illnesses."

This report was introduced at the AMA's Annual policy-making meeting in Chicago.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

JUL 03 2008

Audrae Erickson
President
Corn Refiners Association
1701 Pennsylvania Avenue, N.W.
Suite 950
Washington, DC 20006-5805

Dear Ms. Erickson:

This is in follow up to the meeting of April 16, 2008, between the Corn Refiners Association and the Center for Food Safety and Applied Nutrition (CFSAN). The meeting was prompted by a Food Navigator-USA.com article on the use of the term "natural" on products containing high fructose corn syrup (HFCS). You asked CFSAN to reconsider its position on whether the use of the term "natural" can be used to describe products containing HFCS.

At the meeting Mr. Empie of Archer Daniels Midland Company described the manufacturing process used to make HFCS and following the meeting you sent CFSAN a written description of this production process. During the meeting, we stated that our longstanding policy on the use of the term "natural" is that "natural" means that nothing artificial (including artificial flavors) or synthetic (including all color additives regardless of source) has been included in or has been added to a food that would not normally be expected to be in the food. Additionally, we stated that we do not restrict the use of the term "natural" except on products that contain added color, synthetic substances and flavors as provided for in Title 21 of the Code of Federal Regulations (CFR), section 101.22. After reviewing the information about the HFCS production process that you provided, it is our understanding that the enzyme used to make HFCS is fixed to a column by the use of the synthetic fixing agent, glutaraldehyde. Any unreacted glutaraldehyde is removed by washing the column prior to the addition of the high dextrose equivalent corn starch hydrolysate, which undergoes enzymatic reaction to produce HFCS. Because the glutaraldehyde does not come into contact with the high dextrose equivalent corn starch hydrolysate, it would not be considered to be included in or added to the HFCS. Therefore, we would not object to the use of the term "natural" on a product containing the HFCS produced by the manufacturing process described by Mr. Empie. However, we would object to the use of the term "natural" on a product containing HFCS that has a synthetic substance such as a synthetic fixing agent included in or added to it. We would also object to the use of the term "natural" on a product containing HFCS if the acids used to obtain the starch hydrolysate do not fit within our policy on "natural" as stated above.

For your information, when we received an inquiry from Food Navigator-USA.com asking us whether a "natural" claim on a product containing HFCS and natural ingredients would be misleading to consumers, we reviewed our policy on the use of the term "natural" and our regulations on HFCS. In our response we stated our longstanding policy on the use of the term natural that we described above. We also described our regulation on HFCS (Title 21 of the Code of Federal Regulation (CFR), section 184.1866), which states that it is prepared from a high dextrose equivalent corn starch hydrolysate by partial enzymatic conversion of glucose (dextrose) to fructose using an insoluble glucose isomerase enzyme preparation listed at 21 CFR 184.1372. We indicated that, per 184.1372, the glucose isomerase enzyme preparation is fixed (rendered insoluble) using safe and suitable immobilization/fixing agents, including those listed in 21 CFR 173.357. We stated that the use of synthetic fixing agents in the enzyme preparation, which is then used to produce HFCS, would not be consistent with our policy on the use of the term "natural." Consequently, we said that we would object to the use of the term "natural" on a product containing HFCS. In addition, we stated that the corn starch hydrolysate, which is the substrate used in the production of HFCS, may be obtained through the use of safe and suitable acids or enzymes. Depending on the type of acid(s) used to obtain the corn starch hydrolysate, this substrate itself may not fit within the description of "natural" and, therefore, we stated that HFCS produced from such corn starch hydrolysate would not qualify for a "natural" labeling term. Subsequently, we learned that in the process described by Mr. Empie none of the fixing agent (glutaraldehyde) would come in contact with the high dextrose equivalent corn starch hydrolysate. Consistent with our policy on the use of the term "natural," we have stated in the past that the determination on whether an ingredient would qualify for the use of the term "natural" is done on a case-by-case basis. Further, ingredients with the same common or usual name may be formulated in different ways, where a food containing the ingredient formulated one way may qualify for the use of term "natural" and another food containing the ingredient with the same common or usual name, which has been formulated in a different way may not be eligible for the use of the term "natural."

If we may be of further assistance, please let us know.

Sincerely yours,

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